Molecular biology of oncogenic inflammatory processes. I. Non-oncogenic and oncogenic pathogens, intrinsic inflammatory reactions without pathogens, and microRNA/DNA interactions (Review)

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Abstract. In some inflammasomes tumor cells are generated. The internal environment of the inflammasome is conducive to the induction of malignant transformation. Epigenetic changes initiate this process. The subverted stromal connective tissue cells act to promote and sustain the process of malignant transformation. In its early stages, the premalignant cells depend on paracrine circuitries for the reception of growth factors. The ligands are derived from the connective tissue, and the receptors are expressed on the recipient premalignant cells. The initial events are not a direct attack on the proto-oncogenes, and thus it may be entirely reversible. Epigenetic processes of hypermethylation of the genes at the promoters of tumor suppressor genes (to silence them), and deacetylation of the histones aimed at the promoters of proto-oncogenes (to activate them) are on-going. A large number of short RNA sequences (interfering, micro-, short hairpin, non-coding RNAs) silence tumor suppressor genes, by neutralizing their mRNAs. In a serial sequence oncogenes undergo amplifications, point-mutations, translocations and fusions. In its earliest stage, the process is reversible by demethylation of the silenced suppressor gene promoters (to reactivate them), or re-acetylation of the histones of the oncogene promoters, thus de-activating them. The external administration of histone deacetylase inhibitors usually leads to the restoration of histone acetylation. In time, the uncorrected processes solidify into constitutive and irreversible gene mutations. Some of the pathogens inducing inflammations with consquential malignant transformation contain oncogenic gene sequences (papilloma viruses, Epstein-Barr virus, Kaposi's sarcoma-associated herpesvirus, hepatitis B and C viruses, Merkel cell polyoma virus, *Helicobacter pylori*, enterotoxigenic *Bacteroides fragilis*). These induced malignancies may be multifocal. Other pathogens are devoid of any known oncogenic genomic sequences (mycoplasma *vav*-carcinogenesis, chlamydia MALT-lymphoma genesis). In these cases the host's inflammatory reactions induce the malignant transformation in serial sequences of gene alterations initiated by hypoxia and reactive oxygen and nitrogen species generation. Carcinogenic intrinsic inflammatory processes endogenously initiated without a pathogen are recognized. Chronic inflammatory processes signal the RNA/DNA complex. In response, the DNA may revert into its ancient primordial 'immortal' format, which the clinics recognize as 'oncogenesis'. The DNA remains the ultimate master of bioengineering in order to sustain life. A discussion on the most versatile and resistant primordial RNA/DNA complex and the pre-, proto-, and unicellular world in which they co-existed is included.

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1. Pathogens without oncogenic genomic sequences activating cellular oncogenes

History. Credit goes to Jean-Nicolas Marjolin (1780-1850) for observing and reporting carcinogenesis in chronic fistulous
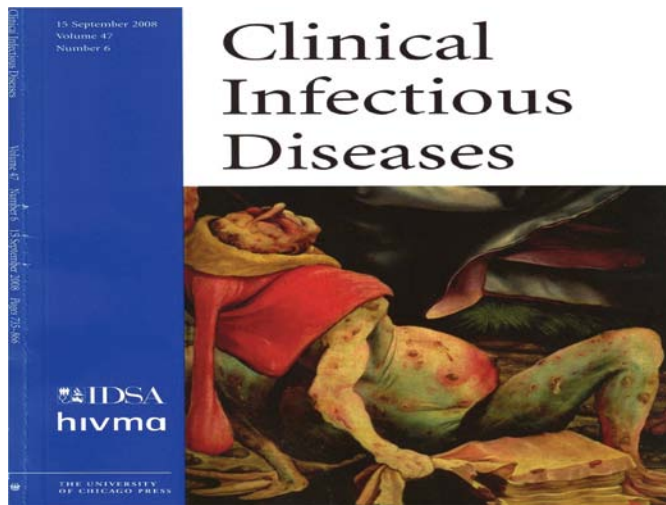
Figure 1. Altarpiece 'The suffering man' by Matthias Grünewald, 1480-1528. Bread baked from wheat infected with *Claviceps purpurea* contained the toxin ergotamine. Consumption of this bread resulted in extensive severe vasculitis and bowel perforations. These patients died with hemorrhagic and septic shock. The 'suffering man' is in the left lower corner of the painting. In the middle (not shown) St. Anthony is praying over the patient. The monks 'Brothers of St. Anthony' stand behind awaiting for their turn to extend help and care to the dying man. Reprinted with permission.

tracts. He described the 'ulcéres verruques' in the hotbed of chronic infections (osteomyelitis with fistulous tracts): 'Ulcére de Marjolin sur ostéite chronique'. He became the Membre de l'Académie de Médicine Français, Paris, France. Contemporary histopathology confirms these lesions to be verrucous squamous cell carcinomas, which may originate in any chronic pustulous infected sites ('ulcéres suppurantes'), like in 'hidradenitis suppurativa' or in anal fissures ('papules péri-anales') and even in gingiva, tongue, and the oropharynx (*vide infra*).

Rudolf Virchow (1821-1902) described the inflammatory environment 'Phlogose und Thrombose im Gefässsystem' of malignant tumors ('die krankhaften Geschwülste'). Recently, Virchow was remembered in the Lancet for his early observation (1863) that chronic inflammatory processes accompany, and may even induce, cancers (1).

Septicemia. The monks 'Brothers of St. Anthony' recognized the high rate of mortality when they attended patients in the 1500's, who suffered hemorrhagic and septic shock after consuming bread baked with *Claviceps purpurea* infected wheat. The alkaloid ergotamine of the fungus caused severe widespread vasculitis further complicated by septic shock, when guts perforated and peritonitis set in (Fig. 1) (2). High early mortality might have eliminated those patients who might have increased their susceptibility to late cancers due to suppressor gene silencing or oncogene activations during the acute illness.

Hemorrhagic and septic shock remained an acute complication of the highest mortality in the practice of medicine, especially when combination chemotherapy was introduced in medical oncology/hematology. This author attended patients with hemorrhagic and septic shock at the M.D. Anderson Hospital, University of Texas, Houston, TX, in the 1960's and 1970's (3-6). Those were the years when a leukemic patient with post-chemotherapy leukopenic fevers could die in pseudomonas septicemia with multiple vital organ failures within 24 h.

A major recognition in the pathogenesis of hemorrhagic-septic shock is the role of the histone deacetylases. Histone deacetylation is balanced by the activities of histone acetyltransferases that transfer acetyl groups from acetyl coenzymes to lysines (K) within the histone molecules. Histone deacetylases catalyze the removal of acetyl groups from the lysins. Histone deacetylases Class I, II, III, IV are preserved from the yeasts on upward in the evolutionary scale. Class I, II, and IV enzymes are zinc-dependent and occupy various intracellular localizations. Class III enzymes (sirtuins) are nicotinamide adenine dinucleotide-dependent. The genes of histone deacetylases are sensitive to inhibitors (HDACIs), and as such HDACIs exert neuro-, cardio-, and renal-protective effects in patients with hemorrhagic-septic shock. In the precancerous state, prominent is the activation of the PI3-kinase/Akt pathway (phosphatidyl inositol, *akt* transforming oncogene from thymic lymphoma of Jacob Furth's high leukemia Ak, later Rockefeller Institute AKR, mice), which is frequently activated as a cell-survival pathway in early events of carcinogenesis. Consequentially to PI3k/Akt activation, insulin-like growth factors (IGF), erythropoietin (EPO) and anti-apoptotic cytokines are activated. At the same time HDACIs inhibit Toll-like receptor TLR4, whose response to lipopolysaccharide (LPS) endotoxins is the activation of IL-1β and MyD88 (myeloid differentiation factor/scaffold) and IRAK (IL-1 receptor-associated kinase). Further suppressive effects of HDACIs are to the anti-apoptotic molecule Bcl-2, and the intranuclear transfer of β-catenin, which are frequently activated in early carcinogenesis. The pro-apoptotic tumor suppressor PTEN (phosphatase and tensin homolog deleted in chromosome 10: 10q23) may be inhibited by HDACIs, but this effect protects cardiomyocytes from apoptotic death. PTEN is an inhibitor of the PI3K/Akt pathway (7,8).

Heat shock protein 70 (Hsp70) is induced by HDACIs, thus it exerts its cell-protective and anti-inflammatory effects. Member of the large family of chaperone Hsp, Hsp70, may protect proteins in cancer cells exposed to chemoradiotherapy. However, 2-phenylethyne-sulfonamide (PES) inhibits this tumor cell-protective effect (9). In squamous carcinoma cells, Hsp70 acting as a binding protein to Bcl-2-associated athanogene-1 (Bag-1) conveyed apoptosis-resistance. Hsp70 and Hsp90 protect metalloproteinase-2 in breast cancer cells and assist cancer cell migration and locomotion. Hyperthermia (or fever) mobilized Hsp70 to promote dendritic cell (DC) maturation, macrophage phagocytosis and pro-inflammatory cytokine (IL-8, IL-12) production (10-12).

Bacterial translocations to mesenteric lymph nodes, liver and spleen occur early in both hemorrhagic and septic shock. Epigenetic gene activations and gene silencing occur in the process. At lysine (K) 4 of activator histone 3, triple methylation (me3) occurs (H3K4me3) and results in silenced post-translational modifications. At lysine (K) 27 of suppressor histone 3, triple methylation (me3) occurs (H3K27me3) and results in up-regulated post-translational modifications (13). Endotoxin-(LPS-) stimulated TLR4 activates myeloid differentiation factor 88, the scaffold protein (MyD88), IL-1β, IL-6, IL-12 and TNFα. Of the IL-1 receptor-associated kinases (*vide supra*) IRAK-1 translocates to the nucleus, where it activates STAT and IL-10. Variant IRAK-1 haplotype associates with nuclear factor κB (NFκB, the reticuloendothelial virus' c-*onc* → v-*onc*, Rel oncoprotein) overactivity; NFκB is liberated, transfers to the

nuclei and through gene activations releases an excess of pro-inflammatory mediators. These events increase the fatal outcome of endotoxin shock (14). Endogenously released alarmins and damage-associated molecular patterns (DAMPs) act as ligands to TLR4. Such endogenous ligands of TLR4 are Hsp70 and some high-mobility group box 1 proteins (HMGB). Some of these reactions occur also early in oncogenesis (15). At the clinics, exogenously administered HDACIs antagonize practically all of these reactions (8). In the patients, it is the HMG protein B1 that performs DNA repair and chromatin modification after DNA damage. However, because of its role in mediating lethal systemic inflammation, HMGB1 is targeted for elimination. In contrast, HMGB1 in protecting against mutagenesis and acting for repairing DNA damage, it reduces or eliminates post-septic shock carcinogenesis, and for these reasons it should be saved (16). Indeed, the rate of post-septicemic oncogenesis does not appear to exceed that of the general population. However, the high mortality and short life span of patients in hemorrhagic/septic shock might have eliminated those individuals who would have had experienced inflammatory carcinogenesis.

Variant IRAK-haplotypes regulate NFκB activation in sepsis and increased NFκB activity carries higher mortality (14), thus eliminating those patients who suffered oncogene activations. The saffron-derived carotenoid, crocetin, suppresses microRNA expression (in rat livers) for tumor necrosis factor α (TNFα), interleukin-1β (IL-1β) and inducible nitric oxide synthase (iNOS), thus alleviating the pathophysiology of the condition (17).

In septic shock, LPS-stimulated dendritic cells (DCs) excessively produce IL-6. MicroRNA 142-3p targets an un-translated region (UTR) of the IL-6 mRNA in DCs and thus reduces IL-6 production. Consequentially mortality in septic shock increases. An oligonucleotide (locked nucleic acid-modified phosphorothioate oligonucleotide complementary to miRNA-142-3p) restores IL-6 production in DCs and reduces mortality (18). This report is difficult to comprehend, because it investigated only one pathway of the most complicated events active in septic shock, where IL-6 may act paradoxically both in pro- and anti-inflammatory contexts, and miRNA-142-3p acts also on lymphocytes and macrophages. Further, microRNAs -9, -21, -146, -147, and -155 are also active participants (18).

An interesting corollary is the function of microRNA-142-3p in connection with the expression of fusion oncogene *mll* and its production of oncoprotein MLL (mixed lineage leukemia). The gene derives from the trithorax homologue of the drosophila; its locus in the human genome is at 11q23. It fuses quite promiscuously with various gene segment partners. When fused with AF4 proto-oncogene segment from 4q31 (asymmetric *fmr2* gene; *fmr2* = fragile mental retardation), it is associated with the induction of pro-B cell acute leukemias of newborn infants (19-21). The microRNA-142-3p targets the 3'UTR (untranslated) fragment of the mRNA from fused gene *mll/af4* (17), thus it exerts anti-leukemia effects.

Epigenetic oncogenesis. Epigenetic events provide a link to oncogenesis and lead to the use of the new terminology 'epigenetic field for cancerization' and 'epigenetic switch linking inflammation to cancer' (22). One of the experimental supports for the use of the new terminology comes from the Harvard Medical School. The activation of the *src* proto-oncogene triggers NFκB-mediated inflammatory response leading to the production of microRNA Lin-28 (lin = cell lineage abnormal in the nematode caenorhabditis and upward) and to the down-regulation of microRNA Let-7 (let = lethal in caenorhabditis and upward). Let-7 being an inhibitor of IL-6 production, its down-regulation leads to increased levels of IL-6. IL-6 activates the STAT3 pathway and further activates NFκB. STAT is an activator of microRNA-21 and miR-181b-1. These microRNAs inactivate the tumor suppressor genes PTEN and CYLD (23,24) (PTEN = phosphatase and tensin homolog on chromosome ten, 10q23; CYLD = cylindromatosis turban tumor suppressor gene on chromosome 16q12-q13).

In inflamed tissues, the short non-coding microRNA-155 inhibits the repair of dsDNA breaks, or allows mismatch repairs. These cells assume the 'mutator phenotype' and overexpress hypoxanthine phosphoribosyl-transferase to reflect to the excessive number of DNS breaks and mutations. Antibiotics (doxycycline), and LPS-induced inflammatory cytokines (TNF family members, IL-1β, IL-6, IL-8) increase microRNA-155 expression in cancer cells. More dsDNA breaks follow. LPS-stimulated macrophage-conditioned medium imitates the effects of microRNA-155. The proliferation rate of adenocarcinoma cells is accelerated by microRNA-155. The cell cycle inhibitor Wee (small, in Scottish, by its discoverer Dr Paul Nurse working in Edinburgh), the *wee* gene product protein, the Wee kinase, is down-regulated by microRNA-155 (25). Thus, microRNA-155 removes the cyclin-dependent kinase (CDK) mitotic inhibitor, allowing uninhibited cell divisions to proceed. An anti-sense microRNA-155 iRNA (interfering RNA) neutralizes microRNA-155. The *wee* gene product protein WEE re-appears and mitoses come to a halt (26). The originally studied *Schizosaccharomyces pombe* cells with active Wee were non-dividing and remained small (wee), whereas the dividing cells (no Wee) were large. The anti-mitotic tumor suppressor gene *wee* is often eliminated in human cancer cells (27). Inactivation of Wee by microRNA-155 is one of the mechanisms of inflammatory carcinogenesis (25-27).

Among other cancers, microRNA-155 is up-regulated in breast cancers. Three microRNAs (miR195, miRNA let-7a, miRNA-155) circulating in the blood of patients are practically diagnostic of breast cancer in 88% sensitivity and 91% specificity (28).

The Argonaute (AGO; the argonautes sailed for king Colchis' Golden Fleece guarded by dragons) family of proteins interacts with mi- and siRNAs and form miRNP complexes that regulate post-transcriptional gene expressions. The ancient AGO proteins in archaea and prokaryotes provide defense against intruding elements (phage genomes, retrotransposons). The modern AGO proteins are essential stabilizing core substances of the microRNA siRNA-induced gene silencing complexes (RISCs) (29,30).

The long intranuclear pri-miRs are processed by the intranuclear enzyme Drosha into 60-70 bp hairpin sequences (pre-miRs). Dicer loads the processed pre-miR sequences into RISCs. The cytoplasmic Dicer enzyme's (RNase endonuclease) substrate, the shRNAs, and/or the siRNAs are loaded into the AGO proteins. In human cells, Ago-2 cleaves the ds siRNA to a ss RNA. The microRNA (mi-R) duplexes also form RISC complexes. Special mi-Rs are able to neutralize mRNAs

traveling into the ribosomes to be translated into oncoproteins (31,32). Nanoparticle cyclodextrin polycations holding siRNAs complementary to the Ewing's sarcoma fusion oncoprotein Ews/Fli1 (Ewing sarcoma breakpoint region I-flightless I drosophila homolog). In a mouse model of metastatic Ewing's sarcoma, this siRNA inhibited tumor growth (33). The CALAA-01 (cyclodextrin-containing polymer, synthetic nanoparticle formulated siRNA, human transferrin ligand aimed at the transferrin receptor) human clinical trial has been approved by the FDA (34,35). The system prevents genomic intrusion, be it viral and/or oncogenic, thus it essentially prevents infection and inflammatory reactions to it, as it destroys the pathogen, be it viral, bacterial, or tumoral mRNAs, before its translation and multiplication.

Cancers originating in scars, chronic fistulous tracts and in lesions of periodontitis. It has been repeatedly observed throughout medical history that burn scars, scars left behind after zoster infections, or small pox vaccinations, chronic purulent fistulous tracts (anorectal, osteomyelytic, non-healing axillary hidradenitis) may convert in time commonly into 'verrucous' squamous cell-, rarely into adenocarcinoma (36-46). Unfortunately the genomics of these tumors were seldom if ever studied; only the documented cytological pathology reports are available as classical examples of inflammatory carcinogenesis: arising as verrucous squamous cell carcinomas in the chronic inflammasome.

There is no accepted proof confirming viral etiology (human papilloma virus, Merkel cell polyomavirus) for Marjolin ulcers or verrucous squamous cell carcinomas. In classical Merkel cell carcinomas, sequences of the viral genome are integrated in the host cell genome, and the viral T oncoprotein is mutated. In cutaneous squamous cell carcinomas of immunocompetent individuals, the polymerase chain reaction (PCR) was used for the detection of Merkel viral genomic sequences including those of the T antigen. Merkel polyomaviral infection was detectable in tumors of epidermodysplasia verruciformis, Bowen's disease, and some basal cell and sqamous cell carcinomas, but without T antigen mutations, or proven viral integration. However, in some squamous cell carcinomas, the Merkel polyomaviral genome was integrated, and the mutated T antigen was truncated. This finding was limited to only of 15% (26/177) of the squamous carcinomas tested (47-49).

At the Roswell Park Cancer Institute, Buffalo, NY, patients with chronic periodontitis were found to experience an increased incidence of squamous cell carcinomas of the tongue and the oral cavity (50,51). Human papillomavirus carriers were not readily recognized (52), but bacteriological cultures point to a particular pathogen, *Porphyromonas gingivalis*. *P. gingivalis* may be dominant, but it is not alone: *Chlamydia* sp. and *Prevotella* sp. are also present in chronically inflamed gingival pockets (53,54a). As a fellow traveler, Epstein-Barr virus (EBV, *vide infra*) was frequently present in lesions of apical periodontitis (54b). *P. gingivalis* induces matrix metalloproteinase-9 (MMP) expression in human oral mucosal epidermal cells and dysregulates the expression of B7-H1 and B7-DC receptors in human gingival keratinocytes and squamous carcinoma cells (55-57). B7-H1, when expressed by DCs, induces the generation of antigen-specific CD4+Fox3+ Treg cells, thus inducing tolerance toward selected antigens. Whereas, down-regulated B7-H1 receptor allows the generation of antigen-specific CD4+ T cell responses and antigen-specific IgG production. In contrast, B7-DC does not bind T lymphocyte-associated antigen CTLA-4; it induces interferon-γ (IFN-γ), but not IL-4 and IL-10 secretion. Thus, B7-DC promotes the anti-tolerogenic Th1-type immunological environment. B7-H1 deficiency results in tolerogenic CD4+ and invariant iNKT cell generation (58-60). The advanced B7 systems are non-existent in teleost and bony fish that are in possession of the VDJ/RAG/RSS (variable, diversity, joining; recombination activating genes; recombination signal sequences) systems. The advanced B7 and ICOS (inducible T cell co-stimulator) systems were acquired later in the evolutionary scale (61,62).

The epigenetics/genomics of squamous cell carcinoma generation. In head and neck and in particular in maxillary sinus squamous cell carcinomas the microRNAs miR-1 and miR-133a close to be knocked out. These are tumor suppressive microRNAs and their elimination is essential for successful carcinogenesis. In contrast, transgelin2 and purine nucleoside phosphorylase levels rise in tumor tissues, when miR-1 and miR-133 are down-regulated. Transgelin-deprived squamous cancer cells ceased to have mitoses and invasive activities (63ab,64). Further, therapeutic interventions influence the composition of tumor infiltrating lymphocytes. Naturally, the chemokine CCL22 invites the infiltration of anti-immune Treg cells. These are the CD4+C25+FoxP3+ tumor-supportive lymphocytes. Hyperthermia treatment encouraged an increased infiltration of both Treg and CD4+CD25- cells. Hyperthermia and irradiation induced only enhanced CD4+CD25- cell infiltration and resulted in decreased Treg cell infiltration without affecting the enhanced CD4+CD25- cell infiltration (65).

The tumor suppressor protein, programmed cell death 4 (PDCD4), exerts also pro-inflammatory effects by up-regulating IL-6 and NFκB production, decreasing IL-10 production, and increasing the mortality of endotoxin (LPS) shock. In contrast, the PDCD4 antagonist, microRNA-21, is activated by the LPS/MyD88/NFκB cascade, or by IL-6 regulated activation of STAT3; then miR-21 exerts anti-inflammatory effects. As miR-21 down-regulates PDCD4, it raises IL-10 levels, thus establishing a PDCD4-deficient tolerogen internal environment. Other NFκB-induced inflammatory cytokines are TNFα and IL-1β. Other consequences of PDCD4 loss is the activation of the PI3K/Akt 'cell survival pathway' commonly used by cancer cells. If an oligonucleotide knocked out miR-21, would the pro-inflammatory (consequentially pro-carcinogenic) effects of PDCD increase? The integrity of PDCD could be protected by preserving its mRNA by morpholino 21 (66).

Both IL-1αβ drive squamous carcinoma cells in the head and neck. Especially, cyclooxygenase-2 (COX-2) is activated. Oncoproteins Snail and Twist promote epithelial-to-mesenchymal (EMT) transitions of the tumor cells. The Snail oncoprotein activates the colony stimulating factor-1 (CSF-1), which attracts macrophages; some of these macrophages convert into the M2/tumor-associated macrophage (TAM) lineage. The proliferation of IL-17/IL-6/STAT3-activated keratinocytes is driven by γδT-17 (IL-17 producing) lymphocytes. IL-17 induces IL-6 production in the macrophages. IL-6 activates 'cell survival cascade STAT3' in the keratinocytes. When IL-17 activates neutrophil leukocytes, endothelial cells and monocytes, it

is pro-carcinogenic. When IL-17 promotes DCs, and activates NK cells and T lineage lymphocytes, it exerts antitumor effects. Tumor cells and their microenvironment with knock-out of STAT3 generate neutrophil leukocytes, and NK and T cells of anti-tumor efficiency. Within reactive DCs, the silencing of STAT3 breaks tumor antigen-specific T cell anergy. A siRNA oligonucleotide and the STAT3 antagonist stattic emerge as clinically effective inhibitors of the STAT3 pathway (67-70).

Patients with intraoral leukoplakia and dysplasia are at risk to advance to have squamous cell carcinoma. The gene CDK N2A encodes the p16^{INK4A} (inhibit CDK4) protein. Methylation of cytosine-post-guanine CpG islands in the genome of the gene silences it. Progression of oral epithelial dysplasia to squamous cell carcinoma begins with the silencing of the p16^{INK4A} gene (71). In squamous cell carcinoma of the nasopharynx, promoter methylations in the CpG islands of the ubiquitin carboxyl terminal hydrolase 1 (UCHL1) gene opens up gates for carcinogenesis. The UCHL1 gene protects p53 and p14^{ARF} (alternative reading frame), which are doomed to ubiquitination, when the gene product proteins are fused (complexed) with the MDM2 protein (named after 'mouse double minus') human homolog gene product protein. The UCHL1 protein de-ubiquitinates the p53 and p14^{ARF} proteins and sends the MDM protein to ubiquitination. The p14^{ARF} protein protects the p53 protein, but only the UCHL1 gene product protein encoded from locus 4p11-14 is able to eliminate MDM2 (72). This is the tumor to whose etiology EBV's latent membrane proteins (LMP, *vide infra*) with or without the human papilloma virus 16's E6 and E7 oncogenes (*vide infra*) so decisively contributed.

Transforming growth factor β receptors II and III (TGFβR) are silenced in the epithelial layer and in the carcinoma-associated fibroblasts of oral squamous cell carcinomas. TGFβI activates through IL-17 an inflammatory reaction in premalignant squamous cell lesions and thus inhibits the growth and metastases of squamous cell carcinomas in the tongue. This very same ligand down-regulated TGFβRII and III, thus promoting tumor progression. The dual role of TGFβ consists of inhibitory effects on tumor growth, and/or tumor growth promotion through activation of myofibroblasts of the tumor microenvironment. The tumor-associated fibroblasts (myofibroblasts) produce keratinocyte growth factor (KGF) and matrix metalloproteinase (MMP) for paracrine receptors of the tumor cells. TGFβ ligands (decapentaplegic, from drosophila) activate the downstream mediator *smad* genes (signaling mothers against decapentaplegic, from the drosophila). Smad signaling operates within the MAPK, NFκB and sonic hedgehog (sHH) network. TGFβ ligands interact with miR-192 and miR377, but antagonize miR-29a; many more such interactions are awaiting recognition (73-76).

Oral cavity squamous carcinoma (OSCC) cells may use an overexpressed autocrine IL-6 → IL-6R circuitry for their own growth stimulation. The growth of human OSCC xenografts was inhibited by the anti-IL-6R humanized monoclonal antibody (mcab) tocilizumab. In the treated animals, the STAT3 pathway, and tumor-directed neoangiogenesis both were inhibited. Further, MMP-9 and IL-8 productions were also ablated. Thus, both autocrine and paracrine tumor growth factor circuitries were targeted by the mcab tocilizumab (77,78). Other inhibitors of OSCC growth factors are anti-IL-8 siRNA; and aspirin and bortezomib for the proteasome/NFκB pathways (78). The strong

efficiency of anti-inflammatory agents against OSCC proves that inflammatory processes initiate and sustain this tumor. In this case again, it is the epigenetics that initiated carcinogenesis. IL-6 induced global hypomethylation of the long interspersed nuclear element-1 (LINE-1), and executed silencing hypermethylations in the CpG islands of the promoters of tumor suppressor genes CHFR (checkpoint forkhead zink finger domain); GATA5 [for full sense and anti-sense GATA5M and GATA5U (79)]; and PAX6 (paired box genes) (80).

Rapidly enlarging OSCC tumor masses extend into avascular and hypoxic environments. These tumor cells can adapt to, and grow, in hypoxic environments. Both hypoxia inducible factors (HIF1 and HIF2) promote tumor cell divisions in hypoxic environments. Patients with tumors showing strong nuclear staining for HIFs experienced shortened overall and tumor-free survivals. Lentivirally encoded anti-HIF1/HIF2 shRNA short hairpin anti-sense molecules 1 and 2 knocked out both HIFs in OSCC xenografts and thus inhibited tumor growth (while shRNA-neg control exerted no such effects). The small molecular inhibitor NSC-134754 inhibited both HIFs in Hippel-Lindau gene-defective kidney carcinomas, thus it should be used for targeting against OSCC (81).

Amplification of 3q is common in squamous cell carcinomas of mucosal origin rising from 37% to 92% in lung, uterine cervix, esophagus and head and neck (H&N) cancers. The locus of amplification in head and neck squamous cell carcinomas is the 3q26-27 region. Against 3% or less in normal mucosa, it rises to 25% in dysplasia and carcinoma *in situ* up to over 56% in invasive carcinoma. In recurrent carcinomas the copy number of the gene amplifies up to 72-90% (82). The suspected gene is a member of the SOX gene family (SRY-related high mobility group transcription factor; SRY = sex-determining region in Y chromosome) (*vide infra*).

Small non-coding microRNAs (miR) and long non-coding RNAs are highly active in squamous cell carcinomas and in their niches. The down-regulated miR-489 is a wide-spectrum suppressor of the activated head and neck squamous carcinoma cell oncogene PTPN11 (protein tyrosine phosphatase non-receptor). The cytoplasmic protein PTPN11 operates through two *src* homology domains (83). The miR-200c in squamous carcinoma stem cells switched off BMI1 signaling (Moloney leukemia virus insertion site; human polycomb gene product protein with tyrosine in its ring finger, instead of cysteine, that inactivates PTEN; degrades ubiquitin-proteasome) (84). When BMI1 was up-regulated, miR-200c levels were low. Overexpressed miR-200c down-regulates oncogenes Snail and ZEB1 (zink finger E box) and N-cadherin, but up-regulates vimentin and E-cadherin (consequentially inhibiting the liberation and intranuclear transfer of β-catenin). The EMT and metastatic movements of squamous carcinoma cells with up-regulated miR-200c were inhibited (85). ZEB1 is the master regulator of EMT (the other EMT-inducer gene product proteins are Snail, Twist, Slug); microRNAs miR-200abc down-regulate ZEB1 (86).

At the 3p14 locus, the FHIT gene (fragile histidine triad) is deleted, while the epidermal growth factor receptor gene (EGFR) is overexpressed in 50% of squamous cell carcinomas. EGFR co-amplifies with CCND1 (cyclin D1) (87). Oncogenes overexpressed in smokers' squamous cell lung cancers are the SOX2 (*vide supra et infra*) and BRF1,2 (transcription factor

IIIB-related factor, RNA polymerase III transcription initiator butyrate response factors) at 8p12 (88). The adenylate- and uridylate-rich elements (AU/ARE) are present in the untranslated region (3'UTR) of the mRNAs. The ARE-binding tristetraprolin proteins (among the BRF1, 2) regulate the expression of cancer- or inflammation-associated proteins by attaching to 3'UTRs of mRNAs for their rapid degradation ('mRNA decay') (89). The mutated BRF genes fail to perform.

In the skin undifferentiated keratinocytes rise from the basal layer up to the differentiated suprabasal layer, where they die to form the stratified barrier lining. The activator protein (AP) transcription factors are part of the complex regulatory process. Inactivation of the AP factors results in hyperproliferation of undifferentiated keratinocytes, which form hyperkeratosis but not tumors (90). The gene product protein E2F (cyclin E inducer factor) brings about the cyclin/CDK2 complex. The E2F1-mediated activation of p19(INK4D) results in the inhibition of CDK4 and CDK6, bringing the cell cycle to a halt in G1. Thus E2F establishes the INK4/pRB/E2F and p19/(ARF)p53 (alternative reading frame) tumor suppressor pathway (91-93).

Inflammation-induced (and other) cancers frequently activate the insulin-like growth factor receptor (IGF-R) pathway, which includes the up-regulated signaling of the Akt (*vide supra*) cell survival pathway (94). Some of the undifferentiated H&N carcinomas with up-regulated IGF-R were EBV+ and/or HPV+ (*vide infra*) (96). Two microRNAs (miR-7, miR-375) target the IGF-R1 mRNA, and thus inhibit the growth of squamous cell carcinomas (94,96). However, promoter gene methylations of miR-375 in tumor-bearing patients annuls this effect (96). Monoclonal antibodies directed at EGF-R or IGF-R (cetuximab, A12, MK-0646, dalotuzumab) exert growth inhibitory effect on squamous carcinoma cell *in vivo*, also in clinical trials (97,98).

Xeroderma pigmentosum (XP). First described by Hebra and Kaposi and again by Kaposi as such, illustrated, in the Wiener Medizinische Jahrbuch, pp619-632, 1882. UV light-induced subcutaneous inflammation and dsDNA breaks remain unrepaired in patients with germ-line deficiencies of DNA repair systems (the defective helicases). The ERCC/TFIIH multi-protein multienzyme system carries out the repair of dsDNA breaks (excision repair cross-complementing; transcription factor for RNA polymerase II and XP helicases). The TFIIH opens the double helix; its enzymes are ATP-dependent helicases, 3-subunit CDK-activating kinases and the cdk. Polymorphisms of the ERCC/XPD system result in the failure of the nucleotide excision repair genes, referred to as excision repair cross-complementing repair deficiency, complementation 2 XPD (ERCC2) (99-102).

UV light-induced inflammatory changes and polymorphism in the nuclear excision repair gene complex increases the susceptibility to basal cell carcinoma (103). In BCC, overexpression of the sHH pathways dominates: HIP (HH interacting protein) overexpression and the deletion of the antagonist dickkopf proteins (from 'fat-head' drosophila) dominate. The WNT (wingless, drosophila), E-cadherin/β-catenin and the mTOR (mammalian target of rapamycin) pathways are activated (104,105). The sHH system was named after the 17-year-old hedgehog escaping from the planet Mobius for continuation of his mischievousness on the planet Earth (Sega video).
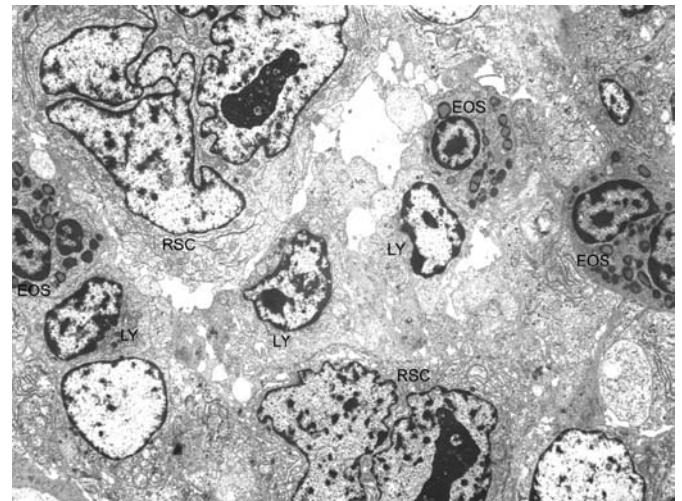

Figure 2. Eosinophil granulocytes in Hodgkin's disease granuloma. The Reed-Sternberg cells are intact, the lymphocytes are inert (refraining from attack). Original magnification, x12,500. Transmission Philips electron microscopy from the material of the Veterans' Medical Center, Department of Pathology (Head, Professor Ferenc Györkey), Houston, TX.
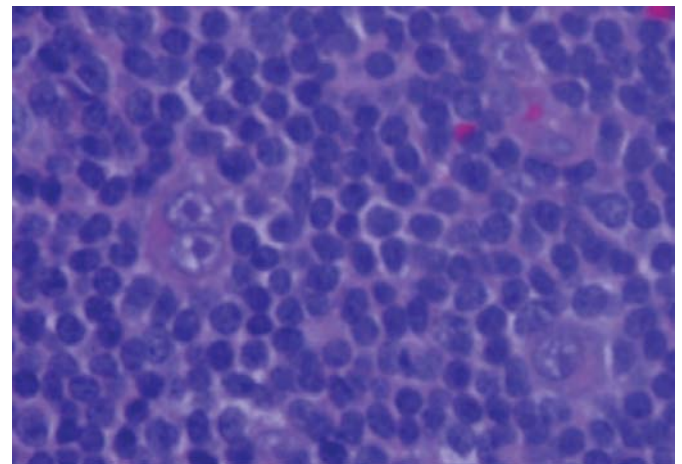

Figure 3. Intact Reed-Sternberg cells in lymphocyte-rich Hodgkin's disease granuloma are surrounded by CD25+ Treg cells for protection against immune T and NK cells. Original magnification, x1,000. From the patient material of St. Joseph's Hospital, Tampa, FL.

2. The inflammasome

An environment conducive to DNA transformation. These ancient formations are the battlefields between invasive pathogens and the host. Microbial molecules (flagellins; LPSs), and the pathogen-associated molecular patterns (PAMPs), are recognized by the Toll-like receptors (TLRs). Granulocytes and monocytes (macrophages) were the defensive cells in the era of innate immunity; so were dendritic cells and NK cells. Eosinophilic granulocytes were selected out as potential defensive cells against inflammatory carcinogenesis (106). If so, they may be failing to defend the host against Reed-Sternberg cells in Hodgkin's disease granulomas (Fig. 2). The Treg cells surround Reed-Sternberg cells protecting them against immune T cells (Fig. 3). Apparently eosinophil granulocytes fail to break through these barriers.

Caspase-1 activates the inflammatory cytokines IL-1β and IL-18 by cleavage into their active form. Alarmin, the high

mobility group B protein is released. By the process of pyroptosis, pathogen-carrier host cells (macrophages) are killed. The pathogens mobilize virulence islands and alter their surface antigenic networks. Poxviruses release soluble IL-1β receptors and IL-18 inhibitors. Multimers are formed by nucleotide-binding leucin-rich repeats-containing proteins (NLRP). The Nlrp3 component invites myeloid-derived suppressor cells (107). Apoptosis-associated speck-like proteins (ASC), caspase recruit domains (CARDs), and transmembrane segments (TMS), also known as ASC and PYCARD (PYD = pyrin domain) are activated. The intracellular nucleotide-binding oligomerization domains (NOD) recognize pathogens that penetrated the cell membrane. IFNγ-producer immune CD8$^+$ T cells are in combat with Treg cells and myeloid-derived suppressor cells (MDSC). Chemokines, on the side of Treg cells, direct them against immune T cells. NLRPs generate MDSCs (reviewed in ref. 108). Outstanding reviews analyze in details the operation of inflammasomes against all classes of pathogens (viral, microbial, fungal, protozoal) (109-113), and all the counteractions of the pathogens, but make no mention just how oncosuppressor genes become silenced and oncogenes become activated within the inflammasomes. However, the figures (cartoons) allow an insight. In the A. Skeldon and M. Saleh paper (111), the appearance of the anti-apoptotic Bcl-2 and Bcl$_{XL}$ proteins could protect incipient tumor cells from apoptotic death. In the P.K. Anand, R.K. Subbarao Malireddi and T.-D. Kanneganti paper (113), NFκB appears as it translocates from cytoplasm to nucleus. This is a common event in oncogenesis, whereby tumor growth factor cytokine genes are activated. There is very little if any mention of epigenomics; reactive oxygen species and dsDNA breaks, etc. The most complex and not uniform composition of the inflammasome may be carcinogenic, or lymphomagenic. The precise mechanisms of intra-inflammasome oncogenesis are not well understood. An attempt at describing these events in the context of inflammatory oncogenesis will be made later in this article.

Mycoplasma oncogenesis. In the mid 1960's, the National Cancer Institute alerted R. Lee Clark, the president of M.D. Anderson Hospital, that reports from European countries (England, France, Germany and Moscow, Russia, then the Soviet Union) claim that strains of *Mycoplasmataceae* are being frequently isolated from the blood and bone marrow of leukemic patients and that these microorganisms may be etiologic (leukemogenic) agents. The British reports were selected out as the most prominent ones (114,115). The reports from Ann Arbor, MI (116) indicated pathogenicity of certain human mycoplasma isolates in mice (toxic deaths, inflammatory conditions, 'leukemoid reactions'). The NCI was to release a substantial special grant for the study of these microorganisms in the context of etiological importance in acute and chronic leukemias. This author was elected to be the principal investigator of the project, based on his earlier publications describing 'pleuropneumonia-like growth of bacteria' (117,118), which elicited a letter and a citation from Joshua Lederberg (119), and an expression of interest in the project by Albert Sabin (120). The pleuropneumonia microorganisms were either true mycoplasmas, or some bacteria growing like pleuropneumonia microorganisms.

A new laboratory was immediately equipped for the growth of mycoplasmas (or pleuropneumonia-like organisms, PPLO) from specimens of human origin (saliva, urine, blood, bone

marrow) collected and provided for the laboratory by the principal investigator, J.G.S. Florence Pipes was recruited from New Orleans to be in charge of the cultures of these microorganisms. Leon Dmochowski, head of the Department of Virology, appointed his technician Bernadette Borchers to prepare the specimens for electron microscopy studies. The principal investigator (J.G.S.) inoculated several hundreds young suckling white Swiss mice intraperitoneally and/or intravenously through a prominent lateral facial vein for observation. The observation consisted of very frequent inspection for 'general health', palpation of lymph nodes and spleens, periodical examination of blood counts and blood smears of the inoculated mice. Mice succumbed early after inoculations showed 'infectious diseases pathology' without any malignant features. However, practically all other mice remained healthy by one full year. Even after sacrificing many of them for internal examination by histopathology, not one case of leukemia or solid tumor (sarcoma, carcinoma) was observed. The cultures of human sources yielded various strains of mycoplasmas in less than 20% of the patients; some mycoplasma-like microorganisms grew out as bacteria (*E. coli*) from patients who were receiving an antibiotic when their blood samples were collected. However, the electron microscopic studies showed spectacular pictures of mycoplasma-like microorganisms (sometimes in cases when the cultures were 'no growth'). The principal investigator's (J.G.S.) report at first year's end was in the 'negative'. Neither the Koch postulates could be verified, nor the oncogenic pathogenicity of the cultured mycoplasma microorganisms (like the most frequently isolated *M. salivarius*) could be proven. In the second year of the project, Dmochowski assumed the position of the principal investigator, as he and Clark suggested to the NCI the need for 'further studies', which remained well financed. In the 4th year's final report of Dmochowski, the conclusion remained in the negative: no leukemo- or oncogenicity of the mycoplasma isolates could be documented by the technology applied (121).

However some 30 years later, a mycoplasma strain, the *M. fermentans incognitus*, emerged as a suspect co-etiologic factor in patients with the acquired immunodeficiency syndrome (AIDS) (122,123). Extensive laboratory studies on this strain of mycoplasma eventually failed to show any unique faculties that would distinguish it from the common other strains of *M. fermentans* (124). Even though, AIDS-related B-lineage highly malignant lymphomas show gene deletions, among them that of the tumor suppressor gene WWOX (double tryptophan WW domain; osteosarcoma oxidoreductase, *vide infra*) (125), mycoplasma microorganisms were not reported (so far) as being visualized in the tissue sections. Now, over 35 years after the negative M.D. Anderson Hospital studies, reports appear of mycoplasma-infected human tumors (adenocarcinomas) in the 40-50% range (126,127). It is recognized that the presence of a pathogen does not mean causation without fulfilling the Koch's postulates.

M. fermentans and *M. penetrans* cultured from patients with AIDS were inoculated into cultured mouse embryo cells at the Armed Forces Institute of Pathology, Bethesda, MD. Progressive multistage malignant transformations (MT) were observed. Early stages of MT were reversed upon mycoplasma eradication with antibiotics (ciprofloxacin). Advanced stages of MT became irreversible (constitutive). Chromosome breaks and deletions were observed during MT, but insertion of mycoplasma genomic

sequences into tumor cell nuclei could not be documented. Tumor cells grew into tumors in nude mice, first very slowly, then in accelerated rate, upon serial passages. Tumor cells showed increased expression of G-coupled proteins, overexpressed chemokine receptors and expressed Ras and Vav oncoproteins. In advanced mycoplasma-induced tumor cells, the Rb and p53 tumor suppressor genes are down-regulated (128-130). Even though the initial oncogenesis occurred *in vitro* in embryonic cell cultures, the authors state: 'Our previous studies have revealed that chronic and persistent infection with these seemingly low-virulence mycoplasmas could gradually but significantly affect many important biological characteristics of mammalian cells and even lead to malignant transformation' (130). However, were innate or adaptive immune reactions generated in the embryonic cell cultures?

The *vav* family proto-oncogenes (*vav*1, 2, 3) show *src* homology, encode nerve cell dendrites, axons and ephrins in Schwann cells in embryonic life, activate NFκB in B lineage lymphocytes, reorganize actin cytoskeletons, act as guanine exchange factors, thus activating Rho GTPases, and accelerate cell mitoses. Vav stands for the sixth letter of the Hebrew alphabet and means 'link' or 'connection'. Vav is emerging as a newly recognized powerful oncoprotein. In an article of spectacular illustrations, Vav is described as guanine nucleotide exchange factor for the Rho (Ras homologous) family GTPases (its *dbl* homology DH domain, the diffuse B large cell lymphoma oncogene), displaying seven other (eight) homologies; among them calponin and pleckstrin homology, zink finger and Src homologies. A truncated Vav is the cell-transforming oncoprotein. The *vav* proto-oncogene was exclusively expressed in hematopoietic cells (and was first found to be silent in epithelial, mesenchymal and neuroectodermal cells). Active *vav* proto-oncogene was detected in some autoimmune diseases (131-136). The human *vav* protooncogene maps to chromosome region 19p12-12.2 linked to the insulin receptor locus (137).

When human malignancies display the VAV oncoprotein: is there a good reason to suspect an etiological connection with prior or persistent chronic mycoplasma infection (with any strain of mycoplasma, or with only the *M. fermentans*, *M. penetrans* strains)? Would serological studies clarify this issue in non-smokers with Vav oncoprotein-positive lung cancers? Or, in patients with Vav oncoprotein-positive prostate cancer and positive serology for genitourinary mycoplasmas (*vide infra*)? Vav1 is expressed in some human lung cancers and Vav3 in some prostate cancers (*vide infra*) (138,139).

Chlamydia lymphoma-genesis. These pathogens notoriously induce chronic infections. In old textbooks these agents were mistaken for large viruses (trachoma virus; psittacosis virus, see in Sinkovics' Die Grundlagen der Virusforschung), but the characteristics of their multiplication was recognized to be that of 'intracellular bacteria, or mycoplasma' (117). *Chlamydia* sp. notoriously infect the uterine cervix and the prostate (140,141). In the uterine cervix, it may co-exist with human papilloma viruses (140).

C. psittaci is a well-established etiological agent of human marginal zone and mucosa-associated lymphatic tissue (MALT) lymphomas. The matter was debated 'against versus for' in Blood with evidence supporting more 'for', than 'against' (142-144).

Periocular adnexal lymphomas are the most common tumors (145,146), but in one case chlamydia-carrier marginal zone lymphoma originated in the choroid plexus of the brain without concomitant periocular involvement. Monocytes/macrophages in the lesions carried the pathogen (147). Chlamydia antigen-driven B cells undergo polyclonal expansion. In this stage oncogenes are not yet activated. The process is reversible by eradication of chlamydia with antibiotics (148). By MALT-like translocations favoring NFκB activation (*vide infra* at *Helicobacter pylori*), monoclonally expanding B cell population(s) emerge (149). The chlamydia heat shock protein (HSP60) released intracellularly exerts anti-apoptotic effect, thus the expansion of the B cell clones continues (150).

B cell clones with the translocation t(11;18) were free of chlamydia, but the NFκB activation remained constitutive. The involved cell clones suffered mutations or deletions of the A20/TNFAIP3 gene (tumor necrosis factor α-induced protein; A20 ubiquitin-modifying anti-NFκB enzyme at 6q, deleted also in AIDS- and EBV-related lymphoma). The gene product proteins of these genes act as suppressors of NFκB. Further, the promoter of the p16/INK4α gene (inhibitor cyclin-dependent kinase 4) was silenced by hypermethylation. The cartoon in the cited article (151) shows genetic predisposition, chronic antigenic stimulation of B lineage cells (once rendered constitutive, the B cell proliferation continues after the disappearance of the antigen of chlamydia derivation), two genetic translocations: t(11;18) and t(14;18), p16 alterations, DC-induced helper T cell generation, autoimmune B cell clones, and constitutive NFκB overproduction (151). With co-authors, this author presented human patients with malignant lymphomas from the clinical material of M.D. Anderson Hospital, in which cases chronic antigenic stimulation (not that of chlamydia) initiated the proliferation of lymphoid cell clones. Some of the antigens were auto-antigens and the lymphoid cell clones acted as foreign grafts attacking the host (causing a graft-versus-host-like autoimmune disease underlying the malignant lymphoma) (152). If an unidentified chlamydia antigen mimics host cell antigens, even after the disappearance of the pathogen, the immune reactions against that antigen may continue both as an autoimmune disease and as a malignant lymphoma. Thus, periorbital B cell lymphomas occurring in Africa (Kenya), but without chlamydia microorganisms being documented in the lesions (153), they still might have been initiated by *C. psittaci*. It appears as if chlamydia initiated *in vivo* an inflammatory process confined to lymph nodes, not carcinogenic, but lymphomagenic.

3. Tumor cell colonies generated in the inflammasomes

Glioblastoma multiforme (GMF). This highly malignant and radio-chemotherapy-resistant tumor expropriated the FasL → FasR pathway for driving cell cycle progression (154). The Fas receptor- (FasR) and granulocyte colony stimulating factor- (GCSF) encoding gene sequences could be artificially recombined *in vitro*. Previously, we presumed that such mismatched fusions of broken chromosomes 1 and 10 occur in melanoma *in vivo* (*vide infra*). These tumor cells undergo mitoses upon capturing FasL. The microglia and astrocytes interact with tumor cells either in an inhibitory or in a stimulatory fashion. It is usually unknown what agents activate these reactions, especially at the earliest tumor-induction phase. In astrocytes

the activated TLR4 induces the ILβ-1/MyD88/NFκB signaling pathway resulting in the mobilization of the 'cell survival' MAPK and Jak1STAT1 (janus kinase) chain reaction (155). Rapidly growing tumors (glioblastoma) advance into hypoxic territories. There, in hypoxic tumor cells, hypoxia-inducible transcription factor HIF1α translocates into the nucleus to bind HIF1β. The HIF1αβ dimer induces neoangiogenesis outside the cell and apoptosis-resistance within the cell. Further, hypoxia responsive elements (HRE) on inflammatory gene promoters (COX, NOS, PTX, CXCR-4, SDF-1α) capture HIF1α (cyclooxygenase, nitric oxygen species, acute phase protein pentraxin, chemokine, stromal-derived factor). In response, tumor cells proliferate (↑ Ki67) and migrate; and resting stem cells undergo activation and enter the cell cycle. These stem cells are vulnerable to malignant transformation instead of differentiation (156).

Adenosine → adenosine receptor A(1)R interactions suppress glioblastoma growth and cellular invasion. A1AR+ microglia cells inhibited the growth and invasion of glioblastoma cells. The nucleoside adenosine derives from the nucleotide ATP. In contrast, A2AR stimulation by its ligand results in the expression of cyclooxygenase-2, prostaglandin and nerve growth factor (NGF). Activated A1AR suppresses MMP production in the tumor (157). These tumors contain microglia cells and macrophages and originate from stem cells (158). In addition to up to 30% microglia in the tumor mass, and some subverted not transformed astrocytes also provide tumor growth factors (159). One of the growth factors is TGFβ acting through its receptor TGFβIIR. Small hairpin complementary shRNA in a plasmid down-regulated expression of the receptor, and thus reduced tumor cell growth and invasiveness in nude mice (160).

J.C. Horvath and this author submitted a hospital surveillance committee-approved protocol for the immunotherapy of GMF with viral oncolysate-stimulated immune T lymphocytes and lymphokine-activated NK cells (LAK cells), which was not funded, for those clinical investigators, who possibly could obtain the financial support (161). This article provided a review on the interactions of astrocytes and microglia with the tumor cells (based on work being carried out up to 2006 at M.D. Anderson Hospital). It concluded that after the eradication of the tumor bulk by surgery and radiotherapy, it will be immunotherapy that will prevent the relapse with resistant tumor cells. At M.D. Anderson and elsewhere, a vaccine of bone marrow-derived dendritic cells pulsed with tumor homogenates was recommended (162,163). A genetically engineered oncolytic adenovirus was another choice (reviewed in ref. 164). The splice variant of the epidermal growth factor receptor EGFRvIII vaccine was already in its earliest clinical trials. The article (161) recommended a viral oncolysate vaccine subcutaneously, and adoptive immune T cell/NK cell therapy to be administered through an Ommaya reservoir into the tumor bed. In support, it was known that the brain readily accepted extravasated immune T and NK cells (165-167). NK cells attack glioblastoma cells (168,169). However, TGFβ inactivates NKG2D cells (170). Adoptive lymphocyte-therapy is a target of Treg cells/MDSCs. While the lymphoid cells (immune T cells, NK cells) kill tumor cells *in vitro*, they are disabled to do so *in vivo*. It appears that postoperative temozolomide and the EGFRvIII vaccine became the current standard therapy, except, tumor cells emerged without EGFRvIII expression, that recurred (171,172).

Inflammatory events are essential in the induction and sustenance of glioblastoma. These events are supported by the alleviating effects of anti-inflammatory drugs on the clinical course of this malignancy. Non-steroidal anti-inflammatory drugs activate the genes NAG-1 (non-steroidal anti-inflammatory drug-activated gene), and growth and differentiation factor (GDF-15) in glioma cells. NAG-1 is usually silenced by dense methylations of its promoter; demethylation restores NAG-1 (173). NAG could stop migration and induce apoptosis (with troglitazone) of tumor (gastric cancer) cells (174). The distant TGF-relative, GDF, may be unpredictable: GDF-15 reduced susceptibility of HER2/*neu*+ breast cancer cells to trastuzumab, and GDF-9 induced EMT in prostate cancer cells (175).

Inflammatory changes in the cerebrum bring about and sustain an incurable tumor of the highest lethality, and of chemoradiotherapy resistance. The most complex genomics of glioblastoma exhibit somatic mutations and loss of heterozygosity in its numerous oncogenes. The platelet-derived growth factor and VGF are up-regulated; tumor suppressors p53, RB and CDKN (cyclin-depedent kinase inhibitor) are deleted (176). An Achilles heal of this tumor is revealed by its epigenomics. The oncosuppressor microRNAs-487ab are down-regulated and the oncoprotective microRNA-502 and microRNA-532 are up-regulated. Two other microRNAs (miR-17-5p and miR-106a) are related to tumorigenesis and survival (177). Could the oncoprotective miR-502/532 be attacked by complementary siRNAs? Will targeted therapy (suppression of PDGF with imitanib, VEGF with bevacizumab, iNOS with mercaptoethyl-guanidine, cyclooxygenase with sulindac sulfide, or indomethacine, etc.) induce remissions, which could be maintained with the immunotherapeutic modalities (vaccines and adoptively administered immune T lymphocytes and LAK cells), which, however, unfortunately seldom if ever are supported outside the NIH/NCI (161).

Papillary carcinoma cells of the thyroid release inflammatory cytokines. The pathogenesis of Hashimoto's autoimmune thyroiditis and its consequences of B cell lymphoma or papillary carcinoma have recently been reviewed, but without being able to recognize the initiator(s) of these conditions (178). The customary chain of events is followed: DCs recognize thyroglobulins and thyroid peroxidases, instruct CD4+ T cells to engage B cells to produce antibodies. The expanding B cell population first is polyclonal, until after one MALT-like B cell clone emerges for monoclonal expansion. In the background, because of CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) gene polymorphism, the inhibitor of autoimmunity becomes deficient. The autoimmune B cell clone shows some rearrangement of its IgM heavy chain locus and may undergo the translocation t(8;14) (q24;q32). Apparently no Treg clones rise to inhibit the proliferation of the autoimmune B cell clone (178,179).

The fusion oncoprotein RET/PTC (re-arranged transformation papillary thyroid cancer) is formed and the MAPK signaling pathway is activated. Elevated levels of nitric oxide synthases (NOS) increased NO levels; vascular endothelial growth factor and its receptors VEGFR-1, -2, angiopoietin-2 and its receptor Tie2 were overexpressed; so was the endothelin-1 pathway (180). The RET oncoprotein activates inflammatory genes within thyrocytes; these are the granulocyte/monocyte growth factor, IL-1β, cyclooxygenase-2, chemokine ligands 2 and 20, IL-8 (chemokine ligand 8), chemokine receptor 4 (CXCR4), extracel-

lular matrix-degrading enzymes and lymphocyte selectin genes, mRNAs and gene product proteins. NFκB and transforming growth factor β (TGFβ) levels are high and protect tumor cells from apoptotic death. The activated STAT pathway drives tumor cell replication and inhibits DC maturation, thus immature DCs establish a tolerant Th2-type internal environment (181). The presence of CD4$^+$CD25$^+$FoxP3$^+$ tumor-associated lymphocytes allowed larger tumors and their locomotion to form lymph node metastases (182).

Further pecularities in autoimmune thyroiditis, the thyroid lymphoma and carcinoma are that: i) The background immunologic milieu of the host is Th1-type, so much so that the inducer T cell clone may turn malignant. The malignant T cell clone was CD8$^-$ but CD3$^+$CD4$^+$TCR$^+$ and chemokine-producer (CXCR$^+$CCR5$^+$) (183). In contrast, is it not so that the antibody producer B cell clone is the product of a Th2-type environment? ii) A combat of the reactive lymphocyte clones results in the appearance of many apoptotic cells (184). The question is who are the killers and who are the victims? iii) The inhibitory signals against autoimmunity derive from the CTLA-4 pathway of T (and B) lineage lymphocytes. However, the CTLA-4 pathway does not appear inactivated, even soluble CTLA-4 receptors circulate and are able to react with their ligands CD80/86 (185). Yet autoimmunity occurs and culminates in a B lineage lymphoma. There is an effort to block CTLA-4 with ipilimumab to induce autoimmunity against tumor cells (melanoma) masquerading for exemption and acceptance as self. However, in an environment of autoimmunity already in existence, papillary carcinoma cells are able to arise and prevail. These questions remain unanswered even in the best and most recent texts (186). The papillary carcinoma cells release the inflammatory cytokines (181). The situation in Greaves' autoimmune hyperthyroidism is better understood. There, autoantibodies to the overexpressed thyroid-stimulating hormone receptor (TDHR) and decreased Treg cells in number and function co-operate with IFNα-producer plasmacytoid DCs that cause apoptotic death of the Treg cells (187). It is still unclear what inflammatory process activates the plasmacytoid DCs in the first place: may be an endogenous retrovirus?

Barrett's esophagus and esophageal adenocarcinoma. Barrett's esophagus (BE) is a premalignant condition consequential to chronic gastroesophageal reflux disease (GERD). BE may be viewed as an inflammasome, which harbors a chronic inflammatory process and the germline mutations of one or all three suspect genes: macrophage scavenger receptor-1 (MSR1, locus at 8p22); adenosquamous cell carcinoma-1 (ASCC1, locus at 10q21-22); and collagene triple helix repeat containing-1 (CTHRC1, locus at 8p22.1-24.22). MSR1 mutations are frequently of somatic, and occasionally of germ-line causation. MSR1 mutation leads to up-regulation of the cyclin D1 gene both in adeno-, and squamous cell esophageal carcinomas (CCND1) (188-190). The major inducer of the inflammatory reactions is deoxycholic acid (DCA); its effects on esophageal carcinoma cell lines (squamous cell carcinoma HET-1A, adenomatous carcinoma SKGT4) were studied *in vitro*. DCA induced IL-8 in both, and IL-1αβ in the adenomatous cell line (191). The tribbles-homology-3 (TRB-3) gene (a gene controlling mitogen-activated protein kinase cascades) (191,192), was induced in the squamous, and silenced in the adenomatous cell line; it was suppressed in most other esophageal carcinoma

cell lines *in silico*. It could be experimentally silenced by small interfering RNA (siRNA) preparations. Re-induction of the TRB-3 gene into the adenomatous cell line resulted in the release of NFκB, a cytokine known to activate inflammatory cytokines upon its intranuclear translocation (190,191). In BE active are IL-6 and signal transducer and activator of transcription (STAT) (192,193), oxidative stress inducible NO synthase (194), cyclooxygenase-2 (195), and prostaglandins (196). In BE, inflammatory gene expression is associated with the activity of miRNA-375. Poor prognosis-associated lymphokines were IFNγ, IL-1α, IL-8, IL-21, IL-23. Co-expression of miRNA-375 improved the prognosis, so did expression of the pro-apoptotic and cell proliferation inhibitor annexin-1 (ANXA1), which was inhibited in most esophageal tumors (197).

In the benign stage of Barrett's esophagus, the artificial induction of intracellular acidification elicited the appearance of reactive oxygen species (ROS) followed by double-stranded DNA breaks. These were detected by immunofluorescence for histone H2AX phosphorylation and were prevented by pretreatment with isothiocyanate-stilbene-disulfonate or acetyl-L-cysteine.

Non-repaired dsDNA breaks are considered to be precancerous events (198). MicroRNAs intervene in esophageal carcinogenesis. In comparison with healthy and cancerous tissues, down-regulated microRNAs in the cancer tissue are considered to be tumor suppressors lost, whereas up-regulated microRNAs are suspect cancer inducers. Elevated level of miR-21 in non-cancerous tissues of patients with squamous cell carcinoma, and reduced levels of miR-375 in cancerous tissues of patients with adenocarcinomas foretold adverse clinical course. This review describes the micro-RNA technology (isolation and quantification) in good details. The very valuable Fig. 2A of the cited article compares adenocarcinoma cancerous tissue and non-cancerous tissue levels (with a typographic error overlooked by the editors): in tumor tissue overexpressed were miR-21, miR-223, miR-192, and miR-194; underexpressed was miR-203. In Fig. 2B, squamous cell carcinoma tumor tissue overexpressed miR-21 and underexpressed miR-375. In Fig. 2A, miR-375 is not mentioned in connection with adenocarcinomas, but in the conclusion it is pointed out to be an adverse prognostic factor for BE-associated adenocarcinomas (199).

Pancreatic adenocarcinoma. Chronic pancreatitis leads to adenocarcinoma induction. In Romanian patients studied at Haţieganu Medical School in Cluj-Napoca (Kolozsvár), Transsylvania, TNFα and IL-6 are the dominant cytokines in that condition. In the malignantly transformed tissue, IL-8 and macrophage inflammatory protein-3α appear in elevated levels (200). In tumorigenesis of the gastrointestinal tract, TGFβ first exerts anti-inflammatory and anti-oncogenic effects. Once a malignant tumor is generated, TGFβ becomes its supporter by promoting its invasion and metastases, and by subverting its stroma for the production of cytokines with paracrine circuitries to receptors of the tumor cell (201). For example, fibroblasts of the pancreatic cancer's microenvironment secreted neuregulin-1 for the phosphorylation and thus activation of Erb3 (epidermal growth factor receptor) and AKT (activated kinase transforming/thymic, also known as protein kinase B) signaling pathways in the tumor cells. Erlotinib and the Erb3-directed mcab MM-121 shut down this pathway and halted the growth of pancreatic

cancer xenografts (202). The sHH oncogenic pathway is active in pancreatic cancer cells. Here stem cell gene product proteins Nanog, c-Myc, Oct-4 (nanogs were the celtic people remaining eternally young, avian myelocytic leukemia oncogene, octamer-binding motif) drive tumor cell growth. A laboratory product small hairpin shRNA is inhibitory to Nanog. Natural products epigallocatechin-3-gallate and quercetin synergistically inhibited the sHH pathway and by overcoming Bcl-2- and XIAP- (X-liked inhibitor of apoptosis) promoted tumor cell death (203). A masterfully constructed cartoon depicts the oncogenic genome within pancreatic cancer cells and the cancer-supporting and inflammatory and immunoevasive activities (cyclooxygenase-, prostaglandin-, and VEGF-production, Treg cells, myeloid-derived suppressor cells and tumor-associated macrophages) of the tumor's microenvironment (204). The tumor cell itself exerts effective immunoevasive maneuvers. Supernatants of pancreatic cancer cells inhibit CD4 T cell proliferation and migration, but induced (failed to inhibit) IFNγ production. However, allowed CD69+ lymphocyte subset expansion (205). The cluster of differentiation marker CD69 characterizes most NK/NKT cells and as such it regulates CD17 lymphocytes in establishing Th-17 type immune environment (206). In imitating Treg cells for the neutralization of immune T cells, pancreatic cancer cells are able to express Fox3 under the inducing effect of TGFβ2. When siRNA suppressed Fox3 expression, the cancer cells secreted IL-6 and IL-8 (that were suppressed when Fox3 was expressed). Mimicking Treg, pancreatic cancer cells antagonized immune T cell clonal expansion (207).

The lectin galectin-3 is targeted by matrix metalloproteinase-7 (MMP-7, matrilysin). MMP-7 levels are high in the blood of patients with pancreatic adenocarcinoma. In mice STAT3 dictates the pace of pancreas adenocarcinoma cell divisions and MMP-7 expression (208,209). The ZIP4 protein (zink transporter protein; Zrt/Irt-like protein: zink/iron responsive transporter) works with IL-6 and STAT in stimulating pancreatic cancer cell growth; silencing it with shRNAs inhibits cancer cell growth (210,211). Of cancer cells growing in holo-, mero-, and paraclones, it is the holoclone stem cells that are most chemoresistant, express most of the stem cell genes and corresponding microRNAs and yield most of the tumor-initiating cells (212). In pancreatic ductal adenocarcinoma cells miR-155 targets and destroys the tumor suppressor p53-induced nuclear protein 1 (TP53INP1). Next, the tumor metastasis suppressor E1A-binding protein (EP300) is neutralized by miR-194, miR-200b, miR-220c and miR-429.

The tumor suppressors DPC/Smad4 (DNA-picked chromatin; signaling mothers against decapentaplegic; decapentaplegic = TGFβ ligand) are knocked out by miR-421 and miR-483. The miR-132 and miR-212 inhibit the binding and neutralizing the E2F protein by RB. The NFκB-repressing factor (NKRF) is neutralized by miR-301, thus liberating NFκB. The 'sprouty homolog' of drosophila, Spry2, is neutralized by miR-27a. The tumor suppressor inhibitor of growth protein ING4 is targeted for neutralization by miR-214. In contrast, those miRs that may act as tumor suppressors (miR-34, a p53 activator; miR-96, a K-ras inhibitor; miR375, a pro-apoptotic stimulator by inhibiting 14-3-ζ and down-regulator of Akt; miR-15a, a wingless drosophila Wnt/β-catenin and fibroblast growth factor-7 inhibitor) (213) remain silent in the inflammatory carcinogenesis process within the pancreas. A detailed tabulation of up- and down-regulated microRNAs in pancreatic cancer with literature citations was made available (214), both references from M.D. Anderson Hospital (213,214).

In the human genome, the promoter gene of the inflammatory cytokine IL-1β undergoes single nucleotide polymorphisms (215), that alone without a specific pathogen may initiate an inflammatory process. The stimulated IL-1 signaling pathway up-regulates the tumor promoters nicotinamide phosphoribosyl transferase and prostaglandin H2 synthase in human pancreatic cancer cells (216).

Oncogenesis in the pancreas shows how an inflammatory process can trigger a cascade of oncosuppressor gene silencing and oncoprotein activation, and that the DNA is a willing partner in the plot. It appears as if in an ancient cross-talk resumed, the RNA mobilizes its forces to rescue the DNA from a host threatened with an impending demise (vide infra).

Inflammatory breast cancer. Lymphangitic loco-regional spread of tumor cells results in the occlusion of lymph channels causing the 'peu d'orange' cutaneous edema. However, there is redness, warmth and pain. No infectious pathogens are present (negative stains and cultures). The host defensive reactions are dominated by scanty monocytic-lymphocytic infiltrates; no eosinophils, no granulocytes, no purulence. It appears to be an endogenously activated inflammatory process ('intrinsic inflammation') without any explicitly recognizable external pathogen. The breast cancer associated BRCA gene-defective cancer cells can not repair, but live with, dsDNA breaks. The repair enzyme polyadenosine diphosphate ribose polymerase [PARP, to be distinguished from PPAR, the peroxisome proliferator (vide infra)] would initiate ssDNA strand repairs. However, PARP inhibitors (olaparib, and the anti-inflammatory cordycepin) send BRCA-mutated breast cancer cells through the apoptotic death pathway.

In a murine breast cancer model, leptin activated the Notch signaling pathway and IL-1 and VEGF/VEGFR-2 overexpression (217). The thymic stromal lymphopoietin (TSLP, a IL-7-like type 1 inflammatory cytokine signaling through TSLP-R in CD4+ cells and thus inducing IL-10 and IL-13 production for a Th2-type host immune environment) promotes the progression of breast cancer cells both by lymphatic and vascular routes. Inactivation of TSLP in a mouse model, resulted in the cessation of all tumor metastases (218). The inflammatory cytokine, TNFα promotes the growth of HER2/neuT breast cancers in mice. Deprivation of TNFα resulted in disarranged tumor vasculature and conversion of Th2-type to Th1-type inner immune environment (unexpected, as TNFα with IFNγ are classical inducers of the Th1-type inner environment) (219). The relevance of these pathways to human breast inflammatory cancers is unknown. However, TNFα-308 polymorphism comes with reduced breast cancer incidence in Caucasian women (220). The polycomb protein, zeste homolog-2 (EZH-2) is overexpressed in human inflammatory breast cancer cells with cell cycle progression resulting. Patients with zeste-expressor inflammatory breast cancer cells had short survivals (221). ErbB1/2 overexpression is also frequent in inflammatory breast cancer cells. The patented lapatinib analog GW583340 induced cytoplasmic ROS (vide infra) formation with apoptotic cell deaths following; these effects were reversed by superoxide dismutase (SOD). Inflammatory breast cancer cells with elevated levels of SOD and glutathione resisted apoptotic deaths due to no H_2O_2 (ROS)

formation upon treatment with the lapatinib analog or paraquat (222).

The infiltration of human breast cancers with CD8$^+$ T lymphocytes is correlated with better prognosis (223). However, a subclass of CD8$^+$ T cells, appears to promote lymphangitic spread of human breast cancer cells toward regional (axillary) lymph nodes. These breast cancer cells undergo EMT. The lymphocytes are of the ILEI subclass (interleukin-like EMT inducers). This subclass of T lymphocytes expresses TNFα and TGFβ and needs the co-operation of mutated Ras and Snail oncoproteins in the tumor cells (224). This author proposed the terminology of traitor/transforming T cells (T/T T) for this subclass of lymphocytes (225). However, no matter how attractive it is to presume it, it is not known if the T/T T subclass of lymphocytes induces the inflammatory type of breast cancer. In cooperation with chemokines CCR4/CCL22, DC-activated and tumor antigen-specific CD4$^+$ Treg cells infiltrate breast cancers and contribute to the cancer's immunosuppressive process (226a).

Gene sequences related to the mouse mammary tumor retrovirus (Bittner virus) occur in human breast cancers (226b), but further proof is needed for the causative, and/or inflammation-inducing effects of these agents. Many human tumors (teratocarcinomas, melanoma, ovarian adenocarcinoma, and malignant lymphomas express endogenous retroviruses, but without solid proof for etiologic connections (225) (*vide infra* at Kaposi's sarcoma).

The Michigan Cancer Foundation's human breast cancer cell line MCF-7 contains cells of the luminal cancer stem cell markers (ESA, CD44^{hi} hyaluronate-binding pro-metastatic adhesion molecule, CD24^{lo} selectin-binding adhesion molecule, CD133$^+$, and chemotherapy-resistance Drug^{RES} MCF-7). Numb-peptide-activated cytotoxic T cells killed CD44^{hi}/CD24^{lo} cancer stem cells. Patients with breast cancer may benefit from treatment with Numb-specific adoptive lymphocyte infusions, or vaccination with Numb peptides (Numb, Notch oncoprotein antagonist, from drosophila) (227). However, if Numb$^+$ cells are eliminated, its antagonist Notch may prevail. Further, in breast cancer cells Numb protects pro-apoptotic p53 from degradation (cited in ref. 228).

The M.D. Anderson team recognized a chain reaction with the pro-inflammatory TNFα activating IKKβ (I κ kinase), which then inactivated the cancer suppressing complex of TSC1/TSC2 (tuberous sclerosis), which usually acts by holding down mTOR. NFκB gets liberated in the process and transits from cytoplasm to nucleus to activate inflammatory and potentially oncogenic genes (229,230). A comparison of the genomics of inflammatory and non-inflammatory breast cancers revealed overexpression of immune system and mTOR pathways in inflammatory breast cancers (231). The Michigan Comprehensive Cancer Center found overexpressed EGFR and disabled p53 genes. More significantly, the RhoC (Ras homolog) GTPase GTP-binding protein gene was overexpressed in 90%, whereas the Wisp3/LIBC tumor suppressor gene (Wnt-induced secreted protein, from wingless drosophila; lost in inflammatory breast cancer) was deleted in 80% of the specimens examined (232). In France, those inflammatory breast cancer stem cells that overexpressed aldehyde dehydrogenase (ALDH) metastasized most frequently. Graphs show high rate of mortality in ALDH$^+$ inflammatory breast cancers (233). However, non-inflammatory breast cancers expressing ALDH also run an adverse clinical course.

Breast cancer stem cells' DNA is highly oncogenic showing 100 to 1,000-fold increased tumorigenicity in xenografts, more than that of the general cell population of the MCF-7 (Michigan Cancer Foundation) established cell line (*vide supra*). The stem cell phenotype is ESA$^+$CD44$^+$CD24$^{+/low}$ (epithelial-specific antigen). The oncogenic stem cell DNA is highly chemoresistant. The cell line under the effect of miR-27b overexpresses the drug-metabolizing enzyme CYP1B1 (cyclophilin). The active miR-21 targets the mRNAs of tumor suppressor genes tropomyosin (TPM1) and PDCD4. The tumor promoter gene pleomorphic adenoma (PLAG) is targeted by miR-200a and miR-224 and the activities of these miRs are curtailed in the oncogenic stem cells (234). A report names six microRNAs that are overexpressed (miR-335, miR-337-5p, miR-451, miR-486-3p, miR-520a-5p, miR-548d-5p) and seven microRNAs (miR-1a, miR24, miR-29a, miR-30b, miR-320, miR-342-5p, miR342-3p), that were down-regulated in inflammatory carcinomas of the breast. However, the exact genomic origins of most of these miRs have not as yet been pinpointed (235). Inflammatory cytokines IFNγ, IL-6, LPS endotoxin, and poly(I:C) activate microRNA-155 in breast cancer cells; miR-155 then activates the STAT and JAK (Janus kinase) 'cell survival' pathways connecting inflammatory immune stimulation with the inception of oncogenesis (236).

The inflammatory COX-2 expression appears early: already active in ductal carcinoma *in situ* (DCIS), catalyzing arachidonic acid to prostanoids. Its inducer is 12-myristate 13-acetate that could be blocked with the flavonoid apigenin (237,238).

The very rare incidence of anaplastic large cell lymphoma (ALCL) beneath silicone breast implants occurred in women receiving the implants for cosmetic reasons (not after mastectomies for breast cancers). The lymphoma cells are ALK$^-$CD2$^+$CD3$^{+/-}$CD30$^+$CD20$^-$CD45$^-$granzyme B$^+$EBV$^-$ T cells of defective T cell receptors. The lymphoma cells express the anti-apoptotic myeloid cell leukemia-1 protein (MCL-1) controlled by microRNA-29 (it suppresses MCL-1 expression). In ALCL, low miRNA-29 levels allow high expression of MCL-1 (providing protection against apoptosis). It is presumed to be induced by unidentified cytokines from histiocytes reactive to silicone particles (239-241).

Non-silicone implant-related ALK$^+$ anaplastic large cell lymphomas overexpress the anti-apoptotic MCL-1 protein (while Bcl-2 is silent). The MCL-1 protein is under the control of microRNA-29a: in ALK$^+$ALCL miR-29a levels are low due to methylations of the miR-29a gene, thus MCL-1 is liberated. In this lymphoma the nucleophosmin (NPM) and ALK genes fuse: t(2;5)(p23;q35), thus creating the NPM/ALK oncoprotein (NPM is nuclear phosphoprotein B23 numatrin). The NPM/ALK oncoprotein activates the PI3K/Akt and mTOR pathways; the reaction chain continues in the constitutive activation of signaling from sHH/GLI (sonic hedgehog; glioma-associated oncogene homolog) (242,243).

Colonic polyps and adenocarcinoma. The classical 'Vogelgram' describes the sequential gene deletions, mutations and fusion oncoproteins that lead to the transformation of colonic polyps into adenocarcinomas (244). In this scheme, peroxisome proliferator-activated receptor δ (PPARδ), a potential tumor promoter, responding to its natural ligands of fatty acids prostacyclins/prostaglandins and active in inflammatory processes,

is suppressed by the product of the adenomatous polyposis coli gene (APC), whose tumor suppressor pathway consists of APC/β-catenin/T cell factor-4 (TCL-4). This pathway is lost to mutations and deletion at 5q21. In the healthy tissues, the APC gene product protein inhibits the complex formation between β-catenin and TCL-4. Among others (c-Myc), PPARδ is another target of the β-catenin/TCL-4 complex (the PPARδ promoter contains the TCL-4 binding sites). PPARδ mRNA levels are high in colorectal tumor tissues, but suppressed by the functional APC. Deleted (or lost to mutation or silencing) are at 17p the pro-apoptotic p53, the Waf1/CIP1 (wild-type p53 activated fragment; cycline kinase inhibitory protein) at 21p, the Dickkopf, the Wnt antagonist, the colon cancer suppressor gene (DCC) at 18q21, the nm23, the non-metastatic gene at 17q21, and the mutated colorectal cancer gene (MCC) at 5q. Point-mutated is at 5q in its codon 12 the K-ras with activation of c-Myc at 8q24. Loss of heterozygosity at 5q21 involves the APC/MCC genes (244-247).

The colonic polyps are 'inflammasomes' expressing great histiocytic, leukocytic and mast cell activities; CXCL12 (stromal derived factor, chemokine) switches from IL-10 to IL-17 and from anti- to pro-inflammatory Treg cells. The advancement of adenomas (polyps) into adenocarcinomas is through an 'inflammatory phenotype' characterized by attraction of leuko-cytes and macrophages into these lesions by IL-8. Knock-out of the pro-apoptotic p53 gene secures cell survival. Paracrine neovascularization is elicited and activation of the cell motility processes by chemokines (CCL20-to-CCR6; up-regulation of cyclooxygenase-2 by CXCL1) initiate the process. Activation of 'cell survival pathways' (STAT, MAPK, PI3K/Akt) overcomes the opposing forces of MyD88 and IL-18 driving the cell to the stage of no return, that is, the switch of stem cell genes away from differentiation to immortalization (recognized clinically as 'malignant transformation'). The proinflammatory genes involved, many TLRs (especially TLR4), and chemokine genes originating from the innate era, are identified: CXCL1, CXCL2, CXCL3, IL-8, CCL5. CCL19, CCL20, CCL21, CCL23, CCL5; and inflammatory iNOS⁺ macrophages are activated (248-253). However, Hanahan and Weinberg omitted inflamma-tory contributions from the list of carcinogenic events. Mantovani *et al* supplemented trait number 7: inflammatory carcinogenesis (254-256).

At the Semmelweis University, Budapest, Hungary, a major engagement is underway for the elucidation of key mecha-nisms in colonic carcinogenesis (257). What goes wrong in the lymphoid follicles receiving stem cell supplements for the regeneration of the colonic mucosal lining? The colonic epithe-lial cell layer is shed and regenerated by an upward flow of new cells in the crypts in rapid successions. The gut-associated lymphatic tissue (GALT) is dispersed as isolated lymphatic follicles (ILFs). ILFs receive bone marrow-derived stem cells (BMDSC) through their blood and lymphatic vascularization. In ILFs, the resident multiple lymphoid elements, dendritic cells, and syncytia of myofibroblasts encounter and interact with the arriving BMDSCs. The ILFs preserved innate immune faculties and as such, are immediately reacting through TLRs. For the repair of mucosal bowel wall damage, ILFs initiate the mobilization of epithelial cells in the crypts (257,258). The contact between ILF cells and epithelial cells is through the Wnt-Lgr5 (wingless in drosophila; leucin-rich repeat containing G protein-coupled receptor 5) pathway. Lgr5 is overexpressed

in metastatic colorectal cancer cells. These cells undergo EMT, either by mobilizing their own Twist and Snail gene product proteins, or by fusing with subverted tumor-associated macrophages (257-260). The colonic mucosa continually is at an inflammatory alert (252,256), that facilitates the switch diverting from the regenerative function in the stem cells, to the process of immortalization (malignant transformation), upon repeated intake of nutritionally introduced chemical toxins.

The commonly present LPSs and TNFα readily activate REL/NFκB. The gene of this ancient transcription factor was discovered in a strain of the avian reticuloendothelial virus (c-*rel* → v-*rel*). NFκB up-regulates TGF-RβII. In colon cancer cells NFκB is constitutively activated. When the NFκB up-regulator IκB kinase γ was knocked out by iRNA, tumor cell xenografts regressed (261,262), The tumor suppressor oncostatin M (OSM) is silenced early in colonic polyps and colon carcinomas. When active, OSM reduces tumor cell prolif-eration, induces differentiation or apoptosis. It is neutralized by DNA methylation, or histone deacetylation. Methyl-transferase inhibition (5-aza-deoxycytidine) and histone re-acetylation (deacetylase inhibitor, trichostatin) re-activated OSM in colon cancer cell lines (263). The microRNA-137 acts as a colon cancer cell suppressor, but early in the process of carcinogenesis, CpG islands of its gene are hypermethylated and thus silenced (264). In contrast, microRNA-21 interacts in a mutual stimu-latory way with inflammatory events (IL-6, IL-8, IL-12a, the tolerogen IL-10, and with the genotoxic NOS2). These actions spelled out a high inflammatory risk score and cancer-specific mortality (265). In mice, inflammation in the bowels mediates the methylation and silencing of the polycomb target genes (for example, lysine 27 on histone 3 was trimethylated) (266). In contrast, reacetylation of histones by histone deacetylase inhibitors (DHDACI, *vide supra*) could induce intrinsic (mito-chondrial) apoptosis of colon cancer cells (267). In Shanghai, P.R. China, a genetically engineered adenovirus delivers the XIAP-associated factor 1 gene (XIAF), which neutralizes the anti-caspase activity of the apoptosis inhibitor XIAP (X-linked inhibitor of apoptosis). The TNF-related apoptosis inducing ligand (TRAIL) is then administered. In colon cancer cell xeno-grafts in mice thus treated, the entire anti-apoptotic machinery (XIAP, c-IAP-2, survivin) was neutralized, and the xenografts were destroyed (268).

The colon is the battlefield between bacteria and bacterio-phages and bacteria and the host (164). Its genomics/proteomics and epigenetics have gone through a very long evolutionary history. Add the uninvited guest, the human polyomavirus JC, whose T antigen inactivates p53, while it liberates β-catenin for intranuclear entry for interactions with proto-oncogenes. It is present in 271/766 (35%) of human colon cancers (269). Now emerges the enterotoxigenic *Bacteroides fragilis*, as a major contributor to colonic carcinogenesis, according to data emanating from the Johns Hopkins' Cancer Institute (270).

The *B. fragilis* enterotoxin cleaves E-cadherin and thus activates the β-catenin/sHH/Wnt cascade. The enterotoxin is neoangiogenic. Colonic mucosal epithelial cells proliferate due to the activation of the STAT/MAPK cascades. Activated NFκB and c-IAP2 (X-linked inhibitor of apoptosis) protect these cells from apoptotic death. The proliferating mucosal cells exude IL-8, an activator of NFκB, cyclooxygenase-2 and prostaglandin. The bacteroides enterotoxin re-arranges the

cytoskeleton of the mucosal epithelial cells. In the process, proto-oncogenes K-*ras* and c-*myc* are activated. Further, the human homolog of the drosophila gene 'legless', the B cell lymphoma gene BCL9 becomes activated. This gene is an activator of the β-catenin/Wnt cascade. The major inhibitor of this cascade, the dickkopf-1 gene product protein is not produced due to the silencing of the dickkopf-1 gene (or its promoter). Some other dickkopf genes (dickkopf-3, -4) are up-regulated; their gene product proteins are neoangiogenic, but the Dickkopf-4 protein is inhibitory to the β-catenin signaling pathway. Other cyto- and lymphokines activated by the bacteroides enteroxin-stimulated colonic mucosal cells are IL-6, IL-8, IL-10 and TGFβ. Cytidine deaminase, TNFα, NFκB, IL-4 and IL-13 somehow eliminate 'the guardian of the genome', p53, in the colonic mucosal cells. Reactive T lymphocytes liberate β-catenin for intranuclear entry. Reactive lymphocytes express T cell factors: TCF-1 promotes, TCF-4 inhibits the Wnt/sHH cascade. Colon cancer cells often express the Fas ligand (FasL+), thus FasR+ immune T cells upon contact with these cancer cells die apoptotic death (extensively reviewed in ref. 62 and original references cited in ref. 270). IL-17 appears. This lymphokine may act as a tumor suppressor, when it activates DCs and NK cells; however, if it activates vascular endothelial cells, granulocytes and macrophages, it acts as a tumor promoter (70). In human CpG island methylator geno-phenotype colon cancer tissue (proven by assaying eight genetic markers), the effect of lymphocytic infiltrates on survival was favorable. The lymphocytes assume Crohn-like, peritumoral, intratumoral periglandular reactions, and tumor-infiltrating patterns (shown in microphotographs). The tumor-infiltrating pattern was associated with significantly improved tumor-specific and overall survival (271).

Further recent reviews of carcinogenesis in ulcerative colitis explain the genomics and proteomics of that condition, the role of IL-13 in the activation of the cell survival STAT pathway (272), but without being able to recognize the ultimate inducing agent(s) (recently reviewed in ref. 62). The highly methylated genes in the inflamed mucosa are the promoter of E-cadherin (CDH1), the transmembrane protein containing epidermal growth factor hyperplastic polyposis (TPEF/HPP), the glial cell line-derived neurotrophic factor (GDNF) and the myoblast differentiation genes (273). Of these genes, CDH1 and HPP exert tumor suppressive functions. This author is impressed by one rare side effect of ipilimumab: 'the hemorrhagic colitis' syndrome. A middle-aged male patient D.L. with metastatic melanoma was sent to the NIH/NCI clinics (Bethesda, MD) to receive a then investigational mcab ipilimumab. While he experienced a better than 50% partial regression of his melanoma, he developed 'hemorrhagic enterocolitis' with perforation and died in septic shock. Even though he received corticosteroids to alleviate his 'autoimmune enterocolitis', at postmortem examination (performed by Dr László Karai), the ulcerated intestinal tract, especially the colon, was infiltrated by lymphocytes (unidentified as to clonality) (unpublished data). The inflammatory reactions in ulcerative colitis are of internal autoimmune causation without an external pathogen. Autoimmune diseases of the gastrointestinal tract involve different organs (pancreatitis with ulcerative colitis) (274). Adenocarcinomas and primary lymphomas of the entire gastrointestinal tract, especially those of the colon with ulcerative colitis, are of autoimmune inflammatory causation (275).

In the non-polyposis colon cancers, Lynch syndrome, inducer genes are named after their ancestors discovered in yeast cells (276): postmeiotic segregation (PMS), mutated S and L homolog (MSH, MLH) (277). In the MSH2-associated Lynch syndrome, the epithelial cell adhesion molecule (EpCAM) gene is also deleted (278,279). In Lynch syndrome, the oncogenic DNA is repaired mismatched. Mismatched repaired DNA proved to be quite viable in the highly malignant transformed cells. Cancers due to germ-line gene mutations may not need much inflammatory stimuli. However, the sporadic mucinous colon cancers arising in hypoxic, inflamed microenvironment are commonly right-sided, multifocal and express the PMS. These mucinous colon cancers are infiltrated by lymphocytes, and express PMS2 gene mutations. In a mouse model, the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) decreased peritumoral colitis and NFκB levels (280).

The intestinal tract suffers from protracted inflammatory processes in ulcerative colitis, Crohn's disease and in non-healing rectal fistulas-fissures (281-283). Polymorphisms of the IL-6 genes, epigenetic methylations of the CpG islands of the WTp53 and KRAS2 genes translate into the CIMP (CpG island methylator phenotype) (*vide supra*). Oxidative-induced DNA breaks initiate and hypoxia-induced inflammation sustains the growing tumor (284-286).

Dietary anti-oxidants (α-tocopherol; β-carotene, the carotenoid, lycopene) and anti-inflammatory agents, aspirin or ibuprofen) are claimed to reduce the rate of inflammatory mutations. Lycopene and tocopherol decreased the rate of p53 mutations; carotens decreased the rate of KRAS mutations. In women, α-tocopherol was protective to p53 against CIMP, whereas in men α-tocopherol was associated with increased mutation rate in these situations. Only in GG IL-6 genotype did high tocopherol levels reduced risks of p53 and KRAS mutations (287).

Prostate cancer. Apart from vertically transferred somatic (acquired), or germ cell mutations (in the minority of cases), this tumor has long been suspected to originate with somatic gene mutations against the background of a chronic inflammation (in the majority of cases). For example, if *Mycoplasmataceae* are carcinogenic by activating the *vav* oncogenes (*vide supra*), could a genitourinary mycoplasma infection be inductive to prostatic adenocarcinoma? Prostatectomy specimens frequently yield (35%) *Propionibacterium acnes*, or corynebacteria, or nanobacteria (288-291), but preceding genitourinary mycoplasma infections in the prostate might have been unrecognized. Calcifications in cancerous breast or prostate tissues may indicate reactions of hydroxyapatite and nanobacteria, if nanobacteria as true life forms really existed on Mars and were transferred to Earth by meteorites (292). As to genetic predisposition and inflammation, the deletion of glutathione S-transferase gene in combination with the histologic picture of 'proliferative inflammatory atrophy' lead to the precancerous intraepithelial neoplasia (293).

Mice transgenic for *vav*3 overexpression (*vide supra*) in the prostate develop NFκB- and PI3K-driven prostate cancers by 3 months of age. These cancer cells also expressed androgen receptor (AR) overactivity. The cancerous glands showed hypervascularity and heavy lympho-mononuclear cell infiltrates. Up-regulation of HER2 and down-regulation of PTEN

occurred. When *vav*3 is activated in the prostate, it may positively interact with the AR, or it may stimulate the growth of prostatic cancer cells independently from AR by activating the PI3K/Akt 'cell survival' pathway (294,295). The human *vav* proto-oncogene was mapped to 19p12-12.2 (137). Vav3 expression was significantly elevated in androgen-independent human prostate cancer cells. A siRNA complementary to *vav*3 mRNA inhibited the growth of both androgen-dependent and independent human prostate cell lines. Molecular inhibitors of PI3K were also effective in inhibiting the growth of *vav*3⁺ prostate cancer cells (296). These authors speak of 'non-bacterial prostatitis' (not to misread as 'nanobacterial'), but do not state if attempts at culturing mycoplasma from the precancerous gland were actually attempted. These authors succeeded in documenting *vav*3 oncogene activation in 81% of the human breast cancer specimens. Vav activated estrogen receptor expressions (297). These studies done at Mount Sinai Hospital, New York and at Albert Sabin Way, Cincinnati, OH, are entirely comparable with similar experiments conducted at the University of Miami's Miller School of Medicine (295,296,298). Here, the Rho GTPase guanine nucleotide exchange factor Vav3 was found markedly increased in androgen-independent human prostate cancer cells. The stimulation of AR by Vav3 protein was active in the presence of subnanomolecular androgens. Thus, Vav3 could maintain prostate cancer cell growth in patients receiving androgen deprivation therapy, which is seldom absolutely complete. Intact pleckstrin strands are KSTR amino acid strings (lysine for K, serine for S, threonine for T, arginine for R, in the substrate of leukocyte kinase C of leukocytes and platelets) obligatory to the activity of Vav3 (298).

A pro-inflammatory condition in the pre-carcinomatous/carcinomatous prostate is consequential to the lipoxygenase product, eicosatetraenoic acid (5-oxo-ETE). H_2O_2 stimulated the increase of 5-oxo-ETE, nicotinic acid adenodinucleotide phosphate (NADP) and glutathione disulfide. Glutathione reductase-dependent generation of NADP was blocked by N-ethylmaleimide (NEM). 5-oxo-ETE exerted strong chemo-attraction toward granulocytes. Granulocytes further released inflammatory cytokines. Arachidonic acid and calcium ionophore induced self-stimulation of granulocytes by 5-oxo-ETE release, that could be blocked by NEM (299). Thus, these chemical reactions could induce prostatitis without a pathogen. A macrophage inhibitory cytokine-1, member of the TGF-family prostate-derived factor is claimed to inactivate suppressor genes and activate oncogenes (300).

Two genes held highly suspect in promoting inflammatory carcinogenesis in the prostate were the ribonuclease L (RNASEL) and the MSR1 genes. Further, the Toll-like receptor family genes and the cyclooxygenase gene have been under suspicion. Finally, single nucleotide polymorphism (SNP) of some lympho- and cytokine genes was considered to be contributory to inflammatory carcinogenesis of the prostate: IL-1β, IL-6, IL-8, IL-10, and the TNF family genes. SNP in four inflammation pathway genes IL-4, IL-6; posttranscriptional gene silencing (PTGS2); and STAT3 were most significantly associated with inflammatory carcinogenesis in the prostate. Aggressive prostate cancers were associated with SNP in AKT1, PIK3R1 (phosphoinositide-3-kinase regulatory subunit 1) and STAT3 genes (301). (Prostatic intraepithelial neoplasia surrounded by heavy inflammatory infiltrate emerges as one of the most adverse prognostic factors. Rider JC, AACR Press release, Sept 27, 2011).

This most versatile tumor may use nitric oxide (NO) for its cells' survival. The plasma membrane molecule carboxypeptidase-D (CPD) obtains arginine from extracellular sources. Arginine is converted to NO intracellularly. Low doses of testosterone or prolactin up-regulate CPD. Through the arginine pathway more NO was generated; these tumor cells gained resistance to apoptotic death (302). NO suppresses Snail and activates Raf-kinase (rat fibrosarcoma) inhibitory protein (RKIP), thus inhibiting EMT of tumor cells (303). The prostate cell genes stearoyl CoA desaturase 1 (SCD1) and the insulin-induced gene 1 (INSIG1) may engage proto-oncogenes, the mesenchymal differentiation inducer gene MAF (musculoaponeurotic fibrosarcoma, MAP) and the Notch receptor ligand jagged (304), thus statins acting on SCD1, and metformins acting on insulin-like GF genes may suppress prostate cancer cells. Some prostate cancer cells de-differentiate toward bone marrow mesenchymal stem cell (305). Promoters of EMT are, among others, the loss of tumor suppressor genes p53 and PTEN (306); β-microglobulins; β-catenin induced by HIF-1α; ester-12 myristate 13-acetate; TGFβ; VEGF; and growth and differentiation factor 9 (GDF-9). Estrogen receptor β (ERβ) expression is suppressed in aggressive high Gleason grade prostate cancer cells. The ligand to the ER, 5α-androstane-3β-17β-diol, maintains the epithelial cell phenotype. Hypoxia and TGFβ suppress ER. Active ER suppresses HIF-1α and VEGF-A. In the absence of ER activity, VEGF-A (neurophilin-1) promotes Snail-1 in the nucleus, which activates vimentin and all other genes to encode the mesenchymal phenotype (307). Prostate cancer cells undergoing EMT metastasize. Most circulating tumor cells display EMT phenotype (308a). Hypoxia, TGFβ and VEGF are notoriously active in the inflammasomes. The inflammatory oncoprotein NFκB activates the *snail* oncogene; the Snail oncoprotein is a major inducer of EMT. The proteasome inhibitor NPI-0052 (nonapeptide inhibitor salinosporamide A from marine actinomycete *Salinospora tropica*), and the NFκB inhibitor DHMQ (same as TMDQ, dimethyl or trimethyl-1,2-dihydroquinoline) repress Snail and reverse the process of EMT (308b).

MicroRNAs miR-143 and miR-145 inhibit EMT and bone metastases; however both miRs are down-regulated in high Gleason grade tumors and thus are inhibited to act (309). In aggressive prostate cancers, miR-221/222 canceled the mRNAs-to-protein translation of p27 (CDKN1B), and p57 (CDKN1C), thus cell growth suppressive cyclin-dependent kinases were silenced. The miR-16 can arrest the cell cycle in G_0-G_1 by negatively regulating (suppressing) HMGA1 (high mobility group) and CAPRIN (cytoplasmic activation/proliferation-associated protein) genes (310). 'The oncogene from hell', c-*myc* → c-MYC, can be silenced by miR-145, except that miR-145 is rendered non-functional in aggressive tumors. Some c-MYC supportive miRs (miR-363, miR-92a, miR-20b, and miR-18b) are up-regulated. Three genes up-regulated in aggressive prostate cancers (Gleason >8) are CCNA2 (cyclin-A2), CDCA5 (cell division cycle-associated) and KIF23 (kinesin family, for rolling movement of the cell nucleus). The two miRs (miR-145 and miR-331-3p) negatively regulating these genes normally, are silenced. When ectopically re-expressed in prostate cancer cell lines, these two miRs exerted growth inhibitory effects (*vide infra*) (311).

The TMPRSS2-ERG gene fusion at locus 21q22 takes place early in prostate cancer cells (transmembrane protease serine 2; ets-related gene; *ets* E26 avian erythroblastosis retrovirally acquired cellular-to-viral oncogene: c-*ets* → v-*ets*) (312). Androgen-signaling brings these two genes into proximity, thus inducing their fusion (313). Altogether, the untranslated 5'UTR region of gene TMPRSS2 (21q22) may fuse with ERG (21q22), ETV1 (7p21), SLC45A3 9 (solute carrier gene) and with HERV-K, the human endogenous retrovirus gene, that in extravillous cytotrophoblasts exerts immunosuppressive properties in the defense of the fetus (314,315). It is the ERG element that dictates the malignancy, even when not fused: patients with increased copy number of the ERG gene in chromosome 21 have a high chance for relapse after radical prostatectomy (316). High expression of HSP-27 encoded from 7q11.23 independently from ETS gene rearrangement (*vide supra*) predicted high risk disease (Gleason >8) and poor prognosis (317). ETS1, ETS4 gene expressions are responsible for anchorage-independent high proliferative tumor cell growth (318).

Another retroviral genomic sequences (and mature virions, in this case) had allegedly existed in some human prostate cancer cells, both in the stroma and in the tumor cells. This is the xenotropic murine leukemia virus-related gammaretrovirus (XMRV). The chain of events is such, that TNFα activates NFκB, which activates XMRV. Herpesviruses are known to activate retroviruses (reviewed in ref. 108) and in the human prostate EBV latent membrane protein-1 (*vide infra*) also activates XMRV. The p65/RelA (reticuloendothelial) component of NFκB attaches to two sites κB-1 and κB-2 in the UT3 region of the long terminal repeat of XMRV. The wild-type XMRV replicates in human prostate carcinoma cell lines, in a Burkitt's lymphoma cell line, and in an EBV-immortalized cell line (319). However, strong new evidence indicates that human prostate cancer xenografts passaged in nude mice picked up two murine proviruses (PreXMRV-1 and 2) which recombined to produce replicating XMRV retroviral particles (320). Picking up murine endogenous retroviruses by human tumor xenografts was observed before (321). The role of XMRV in inflammation-induced human oncogenesis, or in chronic fatigue syndrome, appears to have been negated (320,322). Under these circumstances, it remains a tantalizing puzzle how positive results of viral isolations and serological evidence of human infection with the XMRV could possibly be reported. (High risk 'lethal prostate cancers' xenografted in immunosuppressed mice revealed the well known mutations of the TP53 gene and large numbers of highly individual non-germ-line somatic mutations, 'hypermutations', in DLK2, δ-like homolog, GPC6, glypican-6, and SDF4, stromal cell-derived factor 4, genes; androgen suppression-resistance occurred in Wnt mutated tumors. The individual mutations continued to evolve in the xenografts. (Kumar A, *et al*, press release on Sept 26 from Fred Hutchinson Cancer Research Center, Seattle, WA).

Finally, the B cell-specific Moloney mouse leukemia-sarcoma viral genome's insertion site BMI1 in the human genome remains a point of interest, inasmuch as this site is involved in the activity of stem cells with (or without) the oncogenic activities of the Sox oncoprotein (SRY-related high mobility box family transcription factor; sex-determining region in Y chromosome, *vide infra*). The BMI1 protein is a transcriptional repressor of the polycomb group gene family.

The immunoreactivity of the BMI protein is in the cytoplasm, where it acts as a negative regulator of the cell cycle (Ink4a/Arf, inhibitor cyclin-dependent kinase 4; alternative reading frame), thus cell proliferation. BMI1 is active in stem cells and in several tumors, including gastric and prostatic adenocarcinomas (323,324).

Both stromal and malignant epithelial cells in the prostate gland express keratinocyte growth factor, also known as fibroblast growth factor-7 (KGF, FGF) and its receptor (KGFR). KGF exerts anti-apoptotic (by activating Bcl-2 and Bcl$_{XL}$) and cell proliferation promotional activities (by activating the Akt or MAPK pathways) (325,326ab). While KGF induces differentiation into epithelial basal cells, it promotes AR expression (327). The LNCaP human prostate cancer cell line does not express KGF, but its exposure to external KGF promotes its growth; this is antagonized by flutamide or activin A or vitamin D3 analogs V and BXL-628, Université Libre de Bruxelles (328ab-330). AR is readily activated in prostate cancer cells by IGF, EGF, and KGF (331). Several human established prostate cell lines exhibited malignant growth without expressing KGF/KGFR (332), but high Gleason grade and metastatic tumor cells were KGF- and/or KGFR-positive (333). Benign prostatic hyperplastic cells were negative, but 65% of human prostate cancer tumors were positive for KGF expression, especially in their hormone-insensitive stages (334). From these data, it appears that in benign prostatic hyperplasia, whether chronically infected or not, there is very little if any KGF activity, whereas the appearance of KGF activity signifies advanced and probably hormone-resistant disease. The rare paraneoplastic syndrome, bilateral palmar hyperkeratosis with prostate cancer (335) could be an adverse prognostic sign, especially if persists during therapy.

The WW (double tryptophane) domain contains oxidoreductase. The WWOX tumor suppressor gene is best understood in its relation to Tax oncoprotein of the human T cell leukemia virus, HTLV-I, and osteosarcomagenesis. While the HTLV-I Tax oncoprotein activates the NFκB pathways, WWOX inhibits the HTLV-I/Tax/NFκB pathway (336). In osteosarcomagenesis, WWOX is frequently absent (silenced; mutated). Active WWOX neutralizes the RUNX2 oncoprotein (runt box transcription factor) (337,338). Transduced adenoviral and lentiviral vectors are available for attempts at correcting WWOX deficiency. Tested in xenografted human breast cancer cells, WWOX was either re-instated through the adenoviral vector, or reactivated by the de-methylating agent 5-aza-deoxycytidine. Active WWOX inhibited tumor cell growth (339). Naturaly, WWOX is activated by its ligand PPXY (P = proline, Y = tyrosine, X = any amino acid, W = tryptophane) (340). WWOX is suppressed in adenocarcinomas other than that of the breast (osteosarcoma, colon cancer, small cell carcinoma of the lung, prostate cancer) (336,337,341-343). In small cell carcinoma, it is the BmI1 protein (*vide supra*) that suppresses WWOX (342). In prostate cancer, active WWOX not only suppressed tumor growth, but actually induced apoptotic deaths of tumor cells, but in actively growing tumors WWOX is silenced (344). Since WWOX suppresses HER2/neu$^+$ breast cancer cells, it was tested against prostate cancer cells expressing ErbB2, equivalent of HER2/neu. The transcription factor Ap2y activates the Erb2/neu promoter. When ErbB2 is active in prostate cancer, it enhances AR expression and promotes hormone-independent growth (343). The tumor cells either function on minuscule

amounts of testosterone, or activate their own testosterone production, the ligand for an autocrine loop (AR). The tumor cell carries out the conversion of adrenal androgens into testosterone and dihydrotestosterone and is able to synthesize androgens from cholesterol; these reactions are enhanced by insulin (344,345). These androgens as ligands bind the AR in an autocrine circuitry. Cytochrome enzymes P (CYP) are active in this conversion. The CYP enzymes can be antagonized by abiraterone, but they can gain abiraterone-resistance (344).

The Sprouty 1 (Spry1) gene product protein is a tyrosine kinase receptor inhibitor for the fibroblast growth factor (keratinocyte growth factor, *vide supra*). Prostate cancer cells down-regulate Spry1 both by hypermethylation of its DNA, or by silencing its mRNA by targeting it at its 3'UTR region with microRNA-21 (345). The high cysteine-rich protein gene (HPCX) encoded from locus Xq27-q28 is considered to be a susceptibility gene in hereditary prostate cancer. It is closely associated with genes SPANX (sperm protein associated with nucleus) and MAGE-C1 (melanoma antigen gene protein). The SPANX genes exhibit frequent gene deletions, duplications, homology-based sequence transfers and recombinations. The MAGE-C1 gene's mRNA offers 12 target sites to miRNAs. Gene MAGE-11 resides at Xq28; its protein product belongs to the 'cancer-testis antigen family'; it increases the transcriptional activity of the AR. AR is mapped to Xq11-12 (347-350a). The ectopically expressed super elongation complex gene SEC23A reduced the growth rate of human prostate cancer cell lines without inducing apoptosis. When its mRNA was targeted by microRNAs miR-200c and/or miR-375, this inhibitory effect was abolished (351). There appeared a report on genes in the prostate, which are activated by inflammatory events (301). Of the genes reviewed here, only SPANX appears to be labile and versatile enough to be up-regulated by an inflammatory process. The most recent assessment lists those genes that foretell aggressive disease, relapses and prostate cancer-related deaths. These genes are LEPR (the leptin receptor gene), CRY (the mammalian clock cryptochrome gene), RNASEL (the ribonuclease L gene; latent endoribonuclease, pro-apoptotic unless suffered gene polymorphism), the IL-4-gene, and the ARVCF (armadillo repeat protein deleted in velo-cardio-facial syndrome gene, δ catenin genes, neurojungin, plakophilin, plakoglobin genes) (352). Except for IL-4, the reactions of these genes to inflammatory signals is not well defined at all. The ARVCF gene family is best understood in the context of the metazoan evolution of the catenin gene family (353). The epigenomics of prostate cancer-associated genes (methylation and de-acetylation) (354), and the relationship of gene-derived mRNAs as targets for microRNAS reveals extraordinary complexity. MiRNA-141 levels correlated with those of PSA, lactic dehydrogenase, and circulating tumor cells during the clinical course of prostatic carcinoma (355). The miRNA-200c is activated by oxidative stress (in the inflammasome); by inhibiting oncogene ZEB, it is more of a tumor suppressor gene (356); so it is, when it reduces adenocarcinoma formation in Barrett's esophagus (*vide supra*), or suppresses squamous carcinoma cells in the head and neck region (85,357); but by reducing tumor suppressor Sec23A protein levels, miRNA-200c becomes a promoter of prostate cancer cell proliferation (350a). In comparison, miR-203 is expressed high in normal prostatic tissues, but it is down-regulated in cancerous

tissues. In bone metastatic prostate cancer cell lines, miR-203 is active in inducing the reversal, the mesenchymal to epithelial reaction (350b).

The Sox (*vide supra*) family genes are highly up-regulated in pluripotent embryonic stem cells to maintain clonogenicity, self-renewal and pluripotency, therefore they are active in fetal life. Sox9 is expressed in intestinal crypts and hair follicles (sites of high cellular activities). Stem cells in the basal epithelium of the healthy prostate express Sox9. The sHH, Wnt/β-catenin pathway regulates Sox9. Sox9 is highly expressed in hormone-refractory prostate cancer cells. The Sox9 mRNA can be neutralized by shRNA (358). The single exon *sox*2 gene is embedded within a long non-coding RNA at 3q26.3-27, and exists also in an overlapping transcript: Sox2*ot*. The *sox*2*ot* → SOX2OT is transcribed from a highly conserved element. The ncRNA exercises regulatory function over the expression of the *sox*2 genes. In active *sox*2 gene, lysine (K) 4 of histone 3 is trimethylated (H3K4me3); in inactive *sox*2 gene lysine 27 of histone 3 is trimethylated (H3K27me3) (359).

In fetal life, Sox is an inducer of ectoderm and neurogenesis. It is down-regulated (silenced) upon differentiation. Sox2 undergoes amplifications and mutations, for example in squamous cell carcinomas of mucous membranes of the head and neck and esophagus (82). Up-regulated Sox2 with or without Sox4, Nanog, Oc4, BMI-1, and Myc induces adenocarcinomas of breast, endometrium, and prostate (360-363). In the prostatic adenocarcinoma stem cells, Sox2 with Nanog, Oct-4, Myc, Ras, Klf4 (Krüppel-like family transcription factor, from drosophila), Oskar (drosophila oocyte) co-exist and co-act. Sox is a major contributor to the grade of malignancy: with up-regulated CD44 and PSA; apoptosis resistance (without high Bcl-2, but with down-regulation of Ca^{2+} entry), high Ki67 (K index nuclear protein for cell divisions), high Gleason score (8-9-10), and easy transplantability as xenografts. The Sox2 protein was expressed both in the cytoplasm and in the nucleus of the cancer cells. These cancer cells proliferated at an accelerated rate. These cells resisted apoptosis-induction by thapsigargin and cisplatin. In some prostate cancer cells doxycycline induced shRNA release. In mice receiving doxycyclin in their drinking water, $SOX2^+$ tumor xenograft grew very slowly (363).

Sox2 being the major contributor to all these, when its mRNA is neutralized by a complementary short hairpin shRNA, there is a complete reversal of all malignant scores close to normal: drop of Sox protein, restored apoptosis susceptibility, decreased Ki67 due to a standstill of cell proliferation, drop of Gleason score, and loss of growth potential in xenografts (363).

Prostate cancer bone metastases appear 'blastic' (osteoblastic), but osteoclastic bone lytic activity is substantial. The runt-related transcription factor RUNX family proteins (RUNX2, pivotal in osteogenesis) in heterodimers with the Cbf-β protein (C-repeat binding factor; core binding factor) are overexpressed in those prostate cancer cells that metastasized to the bone. These cells have already undergone EMT (364,365). However, when an α_v-integrin antagonist re-arranged the tumor cell surface, E-cadherin expression went up and vimentin expression went down, forcing the cell to present itself with less mesenchymal and more epithelial phenotype, thus with reduced locomotion and metastatic spread (366). The RUNX complex continued to exert pro-metastatic acts. The DNA proviruses of

mouse leukemia retroviruses readily integrated into the *runx*2 locus (367). Regulatory Treg cells maintain Fox3 expression through the protective effect of RUNX/cbf complexes on the Fox3 mRNA (368). The RUNX/cbf complex suppresses the IL-4 silencer gene *Il4*, and thus releases IL-4 production (369). While RUNX maintains Treg and IL-4 levels, when anti-RUNX targeted therapy becomes available for the treatment of bone metastases by RUNX suppression, IL-4 levels and the supply of Treg cells may drop. Tumor cells notoriously utilize IL-4 (tolerance-induction) and Treg cells (immune T cell elimination), thus RUNX inhibition may result in some immunological benefits as well. The mcab denosumab is directed at the ligand of RANK, the activator receptor of NFκB; it inhibits bone resorption by osteoclasts (370). The standard osteoclast inhibitors remain the zoledronic acid preparations.

The oncogenic DNA of high grade prostate cancer cells is endowed with a great deal of biological-hormonal, radio- and chemotherapy resistance. The Dendreon DC vaccine sipuleucel (Provenge), while immunizing against prostatic acid phosphatase, an antigen of minor significance; it barely prolongs life. The PROSTVAC-VF (Bavarian Nordic) contains a poxvirus (vaccinia and fowlpox virus) expressing PSA with immunostimulatory molecules with or without GM-CSF. The PSA-TRICOM induces powerful immune responses, but as yet without significant clinical benefits (371,372).

Oncolytic viral therapy induces stabilization of disease, minor and partial responses (especially by intratumoral injection, that is, into the prostate) and only occasionally complete responses (usually of short duration). Clinically meaningful durable remissions would occur if antiviral immune reactions of the host could be suppressed, or by-passed by using serially and sequentially alternating different oncolytic viruses (164). Naturally oncolytic (Newcastle disease virus, attenuated poxviruses, reovirus), or genetically engineered oncolytic viruses (adenoviruses, herpesviruses, vesicular stomatitis virus, measles virus, etc.) are available in clinical trials (373-389).

Among others, the special AT-rich sequence-binding gene product proteins (Satb1, 2) regulate gene expressions in embryonic stem cells. Nanog is a major determinant of stem cell gene expressions. Nanog^{low} stem cells lose their pluripotency to differentiation into somatic cells. Nanog^{high} stem cells may self-renew, but remain undifferentiated. Low Satb1 protein levels favor the rise of Nanog^{high} stem cells. Satb2 acts by down-regulating Satb1. Both Satb1 and 2 proteins actually bind 5'-flanking sequence of the Nanog gene. Further, in action, the Satb1 and 2 proteins form homo- and heterodimers. Thus, the balance of Satb1/Satb2 directs Nanog in the stem cell toward differentiation, versus the stem cell keeping its pluripoteny persistently (390). The persistence of pluripotency renders the stem cell conducive to malignant transformation. The transcription factor FoxP3 suppresses the Satb gene in breast and prostate cancer cells; its effect is regulated by miR-7 and miR-155 (391). This system is deleted in cancer cells, and is awaiting for its re-insertion by a viral vector. However, the Satb1 mRNAs can be destroyed by a small hairpin RNA. The uniquely prostate cancer specific gene's DD3 (differential display code 3) presence in prostate cancer (DDR3/PCA3) could regulate as a promoter the expression of the shRNA (392,393). An oncolytic adenovirus was constructed to express the gene of SATB1-shRNA under the DD3 promoter regulation. This adenoviral vector expressed the anti-Satb1 shRNA in prostate cancer cells (cultured *in vitro*) and was cytopathic to the tumor cells (394).

The genomic complexity of prostate cancers is extraordinary. While seven genetic patterns have been fairly well sequenced (395), many more remain still unrecognized. In addition to the well known androgenic pathway, prostate cancer cells over-express EGF-R, IGF-R and prolactin receptors (396-399). The appearance of periostin (and tenascin) exclusively in the tumor stroma indicates that they are tumor-induced and as such they should be targeted for therapy (400).

However, this tumor is not targeted as yet with individualized gene therapy. The primary tumor is treated with the 'fits all' radical prostatectomy, or high dose linear accelerator external beam, and brachy-radiotherapy with or without androgen-deprivation therapy. The 'Beaumont regimen' revealed that in high risk disease (Gleason >8) apparently still confined to the gland (always questionable), hormonal therapy (non-curative, palliative) delaying high dose radiotherapy was of disadvantage ('detrimental') (401-403). This is known since 2007, yet androgen-deprivation is still recommended to precede radiotherapy. Unless leuprolide and/or bicalutamide induce tumor cell apoptotic deaths (other than promoting the 'metabolic syndrome' of the patient), the tumor cells arrested in G_0-G_1 survive the radiotherapy (402). These are the metabolically active, but rendered irreversibly stagnant (not replicating), 'senescent' tumor cells. This is the situation in which AR-negative neuroectodermal prostate cancer cells may arise (without producing PSA).

The best results for high risk disease would appear to be the immediate high dose interstitial radiotherapy (iridium Ir-192 source brachytherapy within the gland and its immediate periphery), preceding the external beam intensity-modulated radiotherapy (IMRT). External beam radiotherapy may induce late carcinogenesis (adenocarcinomas, sarcomas) in the pelvis, and brachytherapy in the prostatic urethra (404,405). These tumors probably arise from radiation-induced gene-mutated cells escaping apoptotic death, but without inflammatory etiology. The predicted incidence of radiotherapy-induced tumors is as high as 1/250 at 5 years, and 1/70 at 10 years (405).

For metastatic disease, no curative treatment is available, but various cytotoxic chemo-, or targeted therapeutic regimens with alternating androgen suppression prolong life. Epigenetic interventions (cancer suppressor gene demethylations or histone re-acetylations) hold promise bordering the spectacular, for the restoration of cancer suppressor genes and for the suppression of oncogenes (354,406). For the promise of targeted therapy, abiraterone inhibiting the cytochrome enzyme CYP17A1, and the *src* family kinase-inhibitor, dasatinib, are the examples (407-409). Dasatinib is a wide-spectrum oncogenic kinase inhibitor, acting against the break-point/Abelson fusion oncoprotein (BCR/ABL), platelet-derived growth factor receptor (PDGF-R) and c-KIT (kinase target). However, the sequentially and serially mutated oncogenic DNA switches from those suppressed to several new (more than 3) oncoprotein-driven pathways.

For the promise of improved immunotherapy, ipilimumab releases autoimmune reactions against cellular targets masquerading as 'self' and as such, it could induce durable remissions in cases of prostatic carcinoma (407,409). Subclasses of cytotoxic/cytolytic lymphocytes are able to recognize and attack transforming stem cells. In order to attack prostate stem cell

antigen-expressing senescent prostate cancer cells, the T cell receptor could be re-directed by bispecific antibodies (410,411).

Estimations in the literature put the incidence of inflammation induced cancers in general at the 35-40% range, except for prostatic carcinoma: there 85% for inducing inflammatory somatic mutations, and 15% for various forms of inherited (SNP, gene mutations and familial vertical transfers) etiology. Non-steroidal anti-inflammatory agents and anti-oxidants [aspirin, ibuprofen, celecoxib, curcumin (Anand P, *et al*, Press release from M.D. Anderson Hospital, Houston, TX, Sept 8, 2011), resveratrol, epigallocatecholamine-gallate, licorice roots' triterpenoids' metabolite glycyrrhizin, lycopene, quercetin, pomegranate polyphenols, silibinin, soy isoflavons, vitamin D analogues, etc.] are of some preventive value in reducing incidence, but have no proven clinical efficacy against established disease; however, it is claimed that they improve the efficacy of standard therapy, and in combinations (the anti-inflammatory celecoxib and antiandrogen hormonal therapy) may induce remissions (412). The preventive value of dutasteride is in doubt: indeed it has utterly failed to prevent high grade disease. These data explain the increased attention inflammation-induced prostate cancer, frequent, most versatile, and devastating, received in this article.

Endometrial adenocarcinoma. The menstrual cycles were recognized to be inflammatory processes imitating wound healing and inviting the outpour of inflammatory cells (leukocytes, macrophages, NK cells). Even in the menopausal stage, the endometrium is receiving an influx of estrogens without the counterbalance of progesterone; androgen levels may rise. Carcinogenesis in the endometrium may occur both by the intrinsic (cancer is initiated first and then is supported by inflammatory cytokines), or by the extrinsic (chronic or periodical inflammatory processes induce carcinogenesis) pathways. Inactivation of PTEN and consequential activation of the PI3K, and Akt 'cell survival' pathways follows. Cytoplasmic NFκB is liberated to transfer into the nucleus, where it activates a series of inflammatory genes. Chemokine and cytokine showers imbue the tissues. The first gene to undergo point mutation is the Kras (Werner Kirsten's Moloney virus-induced rat sarcoma). The transforming tissues exude prostaglandins and cyclooxygenases. Irreversible malignant proliferation of the endometrium takes place (413,414).

The Sox4 oncogene at 6p22 encodes the Wnt/sHH oncogene cascade with Notch and TGFβ signaling. Sox4 is under the suppressive control of the non-coding small miRNA-129-2. In cancerous endometrium the CpG islands of miRNA-129-2 are hypermethylated and thus silenced. In response, the Sox4 oncoprotein is up-regulated. Patients with hypermethylated miRNA-129-2 experience poor prognosis and short life expectancy. DNA demethylation (for example, with 2'-deoxy-5-azacytidine) and histone re-acetylation (for example, with the deacetylase inhibitor trichostatin) with resulting restoration of miRNA-129-2 activity promptly stabilize the course of their disease. Sox4 oncoprotein levels drop; cancer cell proliferation falls to a standstill. Patients with stable disease or actual remission experience prolonged survival (361,362).

Melanoma. Ultraviolet light- (UV irradiation-) induced acquired somatic mutations against the background of UV

light-induced subcutaneous inflammation induce this tumor. The inflammatory mechanisms, if any, that induce visceral, or uveal, melanomas, are unknown. Oncogene B-*raf* (rat fibrosarcoma) is the most common mutation encoding a serine-threonine oncoprotein kinase. This oncoprotein kinase induces abnormalities of the mitotic spindles with aneuploidy in the melanocytes (415). This author repeatedly reviewed his experience with this tumor, both at the basic science level and in the practice of medical oncology (416,417). Patients with melanoma express weak tumor-specific immune reactions in addition to the 'non-specific inflammatory background'. In past decades, Bacille Calmette-Guerin (BCG) was widely used to stimulate the anti-melanoma-specifc immune reactions (418). Some human melanoma cells activate an endogenous retrovirus, whose role in the etiology of the disease, and in the induction, or suppression, of host immunity remain unresolved (419-421).

As to pre-molecular medicine era immunotherapy, Newcastle disease virus-, or influenza A virus-oncolysates cancelled or retarded the appearance of metastases after surgical resections of metastatic lymph nodes in stage III disease; in stage IV disease significant prolongation of life was observed in not prospectively randomized patients treated with viral oncolysates (164,422,423). However, overvaccination could be detrimental. Was this due to chronic inflammatory reactions, or overstimulation of leukocytes and macrophages by GM-CSF? Eggermont analyzed the problem in his superb editorial (424). Patients with metastatic melanoma eliminate the Th1-type internal immunological environment and replace it with the actively tumor-tolerant Th2-type setting (425). Through the expression of the ICOS-L/B7H ligand (inducible T cell costimulatory ligand) by melanoma cells, the host generates large tumor-protective Treg cell populations (426).

The broken chromosomes 1 and 10 undergo mismatched fusion encoding the Fas receptor from 10q23-26 on the cell surface, while the cytoplasmic tail is the granulocyte colony stimulating factor encoded from 1p32-34. Capturing the Fas ligand (FasL → FasR) induces mitoses of these melanoma cells (Horvath JC, *et al*, Proc 89th Annual Meeting American Association Cancer Research, New Orleans, LA, 39: 584, abs. 3971, 1998) (427). Glioblastoma cells utilize the FasL → FasR pathway for their divisions (*vide supra*) (154). The malignant cell DNA can use chromosomal breaks and fusions to its own advantage. The malignant cell DNA enlists microRNAs for its propulsion; in melanoma, the miRs-30b/30d silence the intercellular communication enzyme N-acetyl-α-D-galactosamine polypeptide or N-acetyl galactosamine transferase (GALNT7) and induce the lymphokine IL-10 for promoting tumor cell spread in an immunologically tolerant microenvironment (428).

The mcab ipilimumab and tremelimumab, and the mutated B-RAF oncoprotein inhibitor vemurafenib lead the proceedings toward the possible cure of metastatic melanoma.

Sarcoma. The classical tumor with possible inflammatory etiology is the malignant fibrous histiocytoma (429-431). Under the inquiry 'malignant fibrous histiocytoma' PubMed lists several examples of this tumor occurring in a lumbar abscess, in the retroperitoneum, in the thymus, in the kidney, in the spermatic cord, etc. HIF promotes the inflammatory process. In the chronic inflammasome, reactive oxygen and nitrogen

(N-synthase, iNOS) species induce DNA strand mutagenesis. A mutagenic product is 8-nitroguanine. Co-expression of 8-nitroguanine in the nuclei and HIF1α in the cytoplasm of the targeted cell resulted in NFκB-driven sarcomagenesis with adverse prognosis (432).

Inflammatory lymphocytes reactive to sarcoma cells usually represent complex clones of lymphoid elements. Autologous small round immune T cells and autologous and allogeneic large granular lymphocytes (recognized as NK cells) react to sarcoma cells exploring the target in emperipolesis and either practicing tolerance, or launching a cytolytic attack. Cytotoxicity is expressed either (or both) as cytoplasmic lysis, or 'nuclear clumping', a morphological sign of apoptosis (433). In a desmoplastic small tumor cell sarcoma, talcum-induced reactive macrophages attacked tumor cells in the pleural cavity (430).

An established human chondrosarcoma cell line was observed to undergo a slow process of differentiation *in vitro*. The chondrosarcoma cell line was in advanced passages (over 30 transfers in the 5th year of its establishment), thus considered to be free of any healthy stromal cells, including fibroblasts. To the 33rd passage population of the tumor cell line, small compact, and large granular buffy coat-derived lymphocytes (T cells and NK cells) of a healthy donor (JGS) were added. The large often polyploid tumor cells were explored by the donor lymphocytes (in emperipolesis), but suffered very rare incidence of cytolysis or 'nuclear clumping'. Dividing tumor cells gradually yielded elongated fibroblast-like cells in their progeny with single round nuclei without aneuploidy. These cells eventually showed signs of senescence (documented in serial microphotography). The laboratory was experienced in punctually marking and observing cultures with a very good record of avoidance of mix-ups or cross-contaminations (321,434). The unexplained (and held doubtful) 'spontaneous' differentiation of a chondrosarcoma cell line can now be explained by the reaction of PPARγ uniting with their ligands (435). The artificial ligands of the system (the glitazones, indomethacin) are known, but if lymphocytes could deliver the natural ligands, that has not as yet been explored. If found, a balance of sarcomagenesis in the inflammasomes could be envisioned: the activation of oncogenes counterbalanced by re-differentiation of the transforming cells through ligand-activation of their PPARγ receptors. However, the PPARδ pathway (not to be mistaken for the PARP pathway) appeared to be tumor-promoting in adenocarcinomas (*vide supra*). A chain of events were recognized following the growth arrest of chondrosarcoma chondrocytes by FGF beginning with the dephosphorylation of the RB protein p107, and repression of the E2F genes (436).

Retrovirally induced sarcomas dominate in the animal world from fish up to simian hosts (429), but human sarcomas appear as an outstanding exception. Even when retroviral particles are visualized in a human sarcoma, these have not as yet been isolated and identified (431). It is not clear at all how human sarcomas may be induced by inflammatory reactions, and how inflammatory cells (cytolytic lymphocytes) are actually mobilized to attack them (433). One can envision inflammasomes generating sarcomas. However even the most scholarly reviews of inflammasomes abstain from such suggestion (437). Sarcomagenesis in the inflammasome: is it overlooked or is it not happening?

Instead of the expected sarcomagenic retroviruses, two human sarcomas harbor herpesviruses: in multifocal leiomyosarcoma of children EBV, and in all forms of Kaposi's sarcoma, the human herpesvirus-8 (HHV-8, KSHV) prevail. However, both herpesviruses may activate, or co-exist with, endogenous retroviruses (108,433). Herpesvirally induced sarcomas (Kaposi's sarcoma; EBV-induced leiomyosarcoma), evoke their own virus-specific immune reactions (*vide infra*). Weather these immune reactions are defensive against, or promotional to, these tumors, will be best settled, if both directions are recognized to co-exist (*vide infra*).

Concluding remarks. It was in 1972, when Ruckdeschel *et al* described their clinical observation on postoperative empyemas reducing relapses of surgically removed lung cancers (438a). A decade later, postoperative intrapleural administration of BCG not only failed to inhibit, but it possibly enhanced, recurrent tumor growths of lung cancer (438b). Nowadays, inflammation is named in the pathogenesis of lung cancer (439,440) and we construct immunotherapy for lung cancer 'from inflammation to vaccination' (441).

In the 1970's, the re-organized and lavishly supported NIH/NCI for the Conquest of Cancer issued contracts and grants for the 'non-specific immunostimulation of patients with leukemias and solid tumor cancers'. It would be interesting to find out if corynebacteria (*C. parvum*) actually promoted tumor growth. BCG did better: it induced partial regression of some tumors (melanoma, transitional cell carcinoma of the urinary bladder). It became a vogue and a bandwagon to show 5-10% improvements of chemotherapy results, when BCG was added in the case of practically every tumor; it was then 'the state of art' therapeutical intervention. Yet it has been almost completely abandoned. There was a balance to be found between oncogenic and oncosuppressive immune reactions. The oncogenic inflammatory reactions were not immediately recognized or simply overlooked, and the oncosuppressive immune reactions were overestimated.

At that time (the 1960's), the NIH/NCI steadfastly withheld funding for a 'tumor-specific' immunotherapy protocol (viral oncolysates against melanoma and sarcoma) with or without chemotherapy. Grant applications for viral oncolysate vaccine therapy with chemotherapy combination were rejected as 'mutually exclusive and useless'. However, in the last decade over a dozen clinical trials prove that tumor-specific immunotherapy is additive or even synergistic with chemotheapy, as if chemotherapy inhibited the tumor-promoting inflammatory reactions, and opened up an avenue for the immunotherapy to target the tumor: 'Evidence accumulating in support of cancer vaccines combined with chemotherapy' (442).

Considering the impressive documentation of inflammatory carcinogenesis, the induction of any new inflammatory reaction (oncolytic viruses, vaccines) into a tumor-bearing host should be carefully balanced. Oncolytic viruses and vaccines may work best when combined with a moderate chemotherapy regimen (reducing the tumor load and controlling the oncogenic inflammatory reactions). The newly induced inflammatory reaction of a vaccine or an oncolytic virus should be very specific and forcefully directed against its target; it should be re-inforced by chemo-cytokines and microRNAs with the proven reputation to be pro-apoptotic and anti-carcinogenic.
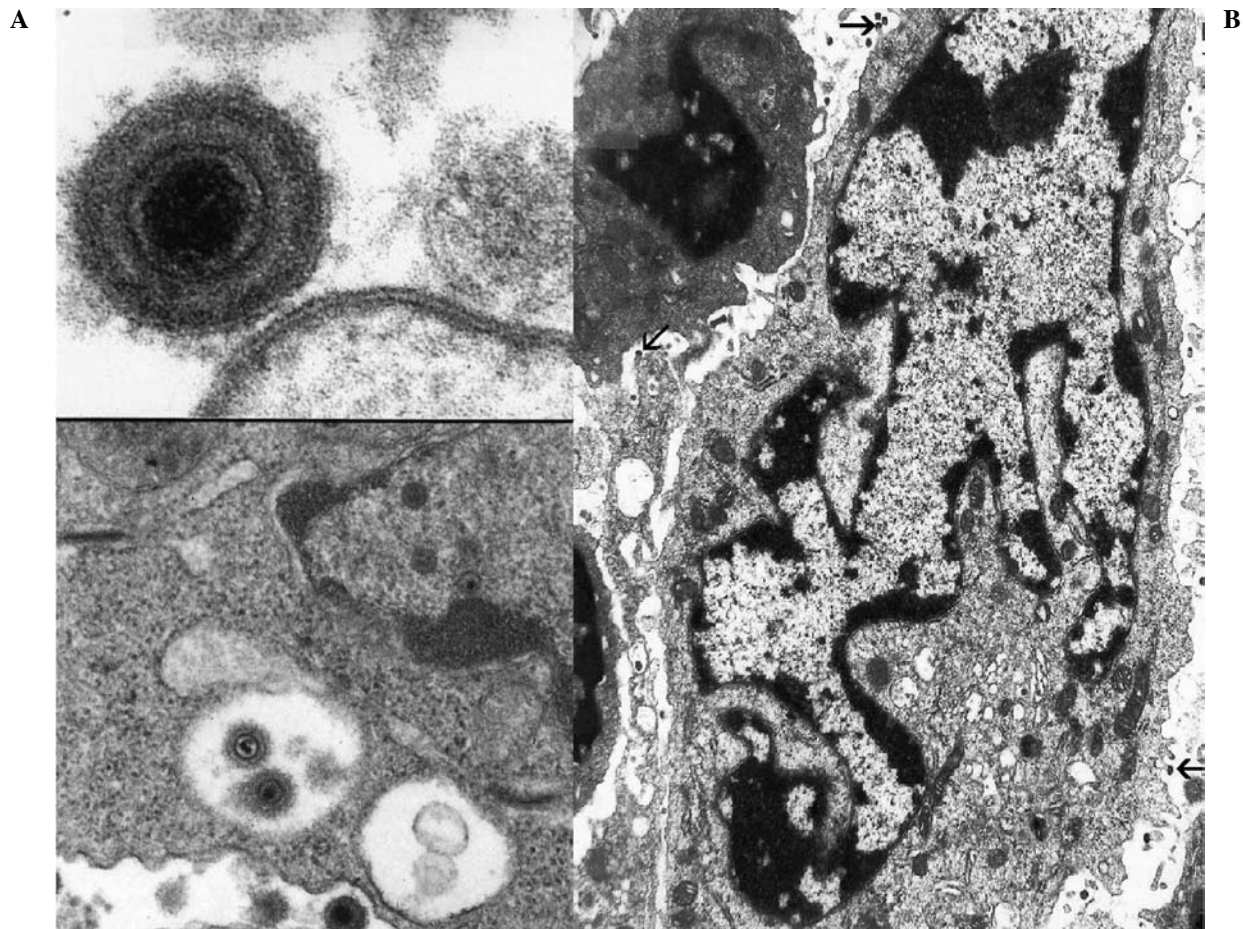
Figure 4. (A), Kaposi's sarcoma cell from the pre-AIDS era shows immature intranuclear, and mature cytoplasmic herpesviral particles (not known then to be HHV-8). Original magnification, x47,500. (B), Budding retroviral particles (not HIV-1) from Kaposi's sarcoma cell of the same patient. The activated endogenous retroviral particles by histochemical stains and attempts at culturing them were not identical with HTLV-I. Original magnification, x16,000. In the case of diminutive reproduction, please use magnifying lens to view the virus particles. Transmission Philips electron microscopy from the material of the Veterans' Medical Center, Department of Pathology (Head, Professor Ferenc Györkey), Houston, TX, USA.

4. Pathogens with potentially oncogenic genomic sequences

Viral I. Kaposi's sarcoma cell nuclei are loaded with immature HHV-8 particles and frequently release an endogenous retrovirus (similar to, but not identical with, human T cell leukemia virus, HTLV-I) (Fig. 4: if printed in a diminutive size, please view under a magnifying glass).

KS-associated herpesvirus (KSHV, HHV-8) reprograms vascular endothelial cells into lymphoendothelial cells (KS cells). The virus infects B lymphocytes and turns them into plasmablasts. Occasionally tonsillary T lymphocytes are also infected. KS cells express the c-Kit (kinase tyrosin) receptor. The major viral oncoprotein is the G protein-coupled receptor (guanyl nucleotide-dependent protein). Open reading frame K12 encodes kaposin A accelerating the MAPK and PI3K pathways, and kaposin B producing endothelial cell regulator Prox 1 (after drosophila gene prospero) (443). The KS cell genome induces anti-apoptotic Bcl-2, down-regulates Rb and p53, induces mTOR and Notch proto-oncogenes, and releases autocrine, or receives paracrine growth factors: IFNγ, TNFα, IL-6 (reviewed in ref. 444). KSHV induces ubiquitin ligases and HIF-1α, thus contributing to the Warburg effect of anaerobiosis (445a). The viral FLICE inhibitory protein FLIP (FADD-like IL-1β converting enzyme, Fas death domain) contributes STAT activation and spindle cell formation. Viral ORF57 encodes vIL-6; its mRNA transcript accumulation (TA) and miRNA recognition elements (MRE) stabilize viral and host cell IL-6 mRNAs (443,445b).

The human interferon (IFN) regulatory factor-related KSHV gene (vIRF-3) inhibits types I and II IFN production in effusion lymphoma cells; it inhibits histocompatibility complex class II expression (thus antigenic presentations). In a peculiar way, IFNγ production was also inhibited (whereas IFNγ was shown to be a growth factor for KSHV) (446,447).

KS cells release 17 adenylated miRNAs. KS miR-K12-7 and miR-K12-7-5p target the 3'UTR of RTA (replication and transcription activator) and the viral immediate early gene, thus maintaining viral latency (448). The genome of KSHV releases 12 microRNAs (miR) from its LANA-associated intron. These miRs post-transcriptionally regulate host cell gene expressions by silencing the corresponding mRNAs. The translation of the miR of thrombospondin is inhibited; thrombospondin is a strong tumor suppressor and anti-neoangiogenic factor (449). The nuclear ribonuclease Drosha-cleaved hairpin RNA exits the nucleus with exportin5, is processed by cytoplasmic ribonuclease Dicer, is incorporated into the RNA-induced silencing complex and thus is guided to the 3'UTR of the targeted mRNA, which is degraded. These viral

miRs have no sequence conservation to metazoan miRs. But the KSHV-induced miR-K12-11 is homologous to the host lymphoma cell-induced miR-155. These miRs regulate the BTB (bric á brac) and CNC (cap'n collar) homology domains, abbreviated as BACH (450-453). BACH-1 is a negative regulator of transcription recognizing antioxidant response elements within gene promoters. In suppressing BACH-1, the membrane-bound subunit of the amino acid transporter xCT increases, thus intracellular glutathione stores remain full providing protection against oxidative stress. Further, xCT is the cell surface receptor for the entry of KSHV (454). The Orf63 of KSHV is homologous to the cellular NLR (nucleotide binding and oligomerization, leucine-rich repeat), which activates innate immune reactions in the inflammasome. KSHV Orf63 protein blocks the cellular NLR at its initiation (IL-1β, caspase-1 and IL-18), thus the virus escapes the activation of innate immunity and its consequences (455).

Classical pre-AIDS KS had the reputation to be a tumor afflicting immunosuppressed hosts (immunosuppressed organ transplant recipients). The classical Southern European patients were elderly. Even in the virulent African KS, an immune system exhausted by bacterial, protozoal and helminthic infections was blamed for the acceptance of these tumors. Severe immunosuppression in HIV-1-infected patients with the acquired immunodeficiency syndrome was thought to render these patients defenseless to these tumors. However, in the most paradoxical way, the recrudescence of virulent KS in these patients after viral inhibitory therapy-induced remission of AIDS with recovery of the immune competence proved that KS could be subject of inflammatory oncogenesis. A long list of references attest to this concept (E.A. Mesri citing articles from Y. Aoki, C. Boshoff, J.L. Douglas, B. Ensoli, R.C. Gallo, P. Monini, L. Pantanowitz, G. Riva, etc.) (456). To the dissatisfaction of this author, these articles speak in generalities and fail to pinpoint the exact tumor-supporting infectious-immunological mechanisms. Constituents of the inflammatory infiltrates around the tumors are listed one by one (DCs, several different classes of lymphoid cells including plasma cells, NK cells, monocytes/macrophages), but without their roles in oncogenesis, or in the defense against it, specified. In patients with KS, immune T cells and cytolytic NK cell are generated, exert cytotoxity to malignantly transformed cells, but eventually fail to control tumor growth (457-459). However, there is recovery from KS, that is regressions of these tumor may occur, for example in organ transplant recipients, when the immunosuppressive medication is withdrawn or modified (460-462). Immunosuppression with rapamycin exerts also anti-tumor effects by the inhibition of the mTOR pathway (mammalian target of rapamycin), thus it may reduce post-transplant Kaposi's sarcoma generation with retention of the graft. HHV-8/KSHV remains in latency failing to enter its lytic cycle in rapamycin-treated virus-carrier cells. Rapamycin specifically inhibits the replication and transcription activator (RTA), the lytic switch protein (463).

Viral II. Dreyfus and Sinkovics independently have made the elaborate suggestion, that an ancestor of the gammaherpesviruses transferred the genomics (genes, operons) into the ancestors of sharks, which in unison for the first time, encoded the adaptive immune system (reviewed in ref. 62). The HHV-4 Epstein-Barr human gammaherpesvirus (EBV) causes infectious mononucleosis; while the infected large B lymphoblasts are rejected by immune T cells, epigenomic latent viral genomes remain silent for the rest of the patient's life. The viral genome persists epigenetically located in memory B cells. EBV contributes to the pathogenesis of lymphoepithelioma-nasopharyngeal carcinoma (type II latency), African Burkitt's lymphoma (type I latency with EBNA-1 expression), NKT cell lethal midline granuloma (type II latency), and Reed-Sternberg cells of Hodgkin's disease (type II latency with EBNA-1 and LMPs expression). EBV immortalizes human B lymphocytes in *in vitro* suspension cultures (type III latency with expression of EBNA-1-6 and LMP1, 2A, 2B); it induces posttransplant lymphoproliferative disease; it induces the EBV⁺ diffuse large B cell lymphoma in the elderly; it is associated with brain lymphomas in patients with AIDS, it is present in multifocal pediatric leiomyosarcomas, and in gastric carcinomas in Japan (reviewed in refs. 62,443). In autoimmune diseases (lupus erythematosus, multiple sclerosis), there is an interaction between EBV and latent endogenous retrovirus(es). Herpesviruses trigger the maturation of latent endogenous retroviruses, which appear budding from lymphoid cells, Reed-Sternberg cells, and even the transformed lymphoendothelial cells of Kaposi's sarcoma (62,108,178,464).

The EBV genome is present in T cells of angiocentric lymphomas presenting as 'lethal midline granuloma' (465), a pathological entity different from the lethal midline granulomas caused by malignantly transformed NKT cells (466-468). In patients with X-linked lymphoproliferative disease with SAP gene mutation (SLAM-associated adaptor protein containing SH2 domain; SH2, Src homology; SLAM, signaling lymphocyte activation molecule), EBV infections are life-threatening (469). It is the tolerogenic, Th2-type immunological environment-inducer IL-10 that activates the expression of EBV's LMP1 in Burkitt's lymphoma and in NK cell lymphomas (470). After EBV infection in healthy individuals, the viral genome rests in a circular configuration in the epigenome. The cytokines IL-4, IL-13 and IL-21, DNA-methylations and histone acetylations-deacetylations control the mode of expression of the latent EBV genome. For the host's health, the most ominous change is the expression of the latent membrane protein (LMP1, 2A, 2B) (471-475).

In order to neutralize host cell mRNAs, which are to be translated into defensive inflammatory proteins, the EBV genome generates numerous (may be over 25) microRNAs (EBERs) (474,475). The EBV genome BamHI-A rightward fragment (BARF) and BamHI (*Bacillus amyloliquefaciens* endonuclease) fragment H rightward open reading frame (BHRF1) release the viral microRNAs most frequently in the case of type III latency in nasopharyngeal tissues. EBV miRNAs target chemokine CXCl-11, inhibit transition from latent to lytic viral replication, and suppress the p53 up-regulated mediator of apoptosis (PUMA), and regulate the expression of LMP (476). The N-terminus of the BARF protein activates Bcl-2 and proto-oncogene c-myc. Soluble BARF protein imitates a CSF and thus is mitogenic; it suppresses IFNα production. Gammaherpesviral miRs are orthologs and interrelated (shared seed sequences) among Marek's disease HV of turkeys, KSHV and others (miR-155) (477).

IL-4 and IL-13-induced STAT pathway elicits EBV's LMP induction (471-473). LMP is a proto-oncogene. EBNA-2 and

EBNA-5, IL-10 and IL-21 induce LMP expression. The truncated LMP transforms and immortalizes B cells and activates Bcl-2, NFκB, STAT-1 and JAK3 (janus kinase). LMP suppresses pro-apoptotic p53 and Bax signals (Bcl-2-associated X protein). LMP induces miR-29b, and thus down-regulates TCL1 (T cell leukemia) oncogene (478). The negative regulation of an oncoprotein by EBV LMP must have some so far unclear biological implications. LMP2A activates PI3K/Akt/mTOR pathways. In a mouse model of Burkitt's lymphoma with c-*myc* translocation, rapamycin suppressed splenomegaly and tumor metastases (479). Host *snail* and *twist* gene activations lead to epithelial-to-mesenchymal transition of EBV-infected cells in NP carcinoma. Translocated β-catenin from cytoplasm to nucleus activates proto-oncogenes (480). LMP1 increases intranuclear transfer and accumulation of β-catenin (481). The LMP of EBV activates STAT protein kinase C (PKC) and ERK (extracellular signal regulator kinase) (482). Malignantly transformed cells operate these very same signaling pathways.

In the EBV granuloma/inflammasome there are lymphoid cells infiltrating (CD8⁺CD4⁺ T cells and CD4⁺CD25⁺Fox3⁺ Treg cells, NK cells, B lineage cells depositing immunoglobulins), mast cells, neutrophil and eosinophil leukocytes and inflammatory lymphokines (IL-1β, IL-3, IL-6, IL-8) and chemokines (CXCL1, the IL-8 analog, CXCL22, CXCL5-6), further, RANTES and MCP1 (regulated on activation normal T cell expressed secreted; macrophage chemoattractant protein) and NFκB and TNFα lubricate the interstitium. These agents one by one or in unison maintain an inflammatory environment serving the virus and the tumor to the disadvantage of the host (483).

EBV-associated multifocal smooth muscle tumors occur worldwide and target children. These tumors are now being recognized in Singapore as leiomyosarcomas in EBER⁺ immunosuppressed kidney transplant recipient adults. EBV latency was considered to be type II (*vide supra*). The tumors persisted and advanced after the discontinuation of the immunosuppressive medication (cyclosporine and prednisone). The tumors activate the mTOR/Akt pathway of oncogenesis. The Ras association domain family gene (RRASSF1A) was methylated (considered to be silenced) and the MGMT gene (methylguanine-DNA methyltransferase) was hypomethylated (yet considered to be silenced) in every case. It is known that EBV LMP attacks (suppresses) RASSF1A. The mTOR inhibitor sirolimus (rapamycin) induced remission in a patient with a leiomyosarcoma in the liver. The tumors were chemotherapy-resistant. Demethylation of the RASSF1A gene could be attempted, however, demethylators can liberate the latent EBV genome (484). A lung transplant patient developed EBV⁺ uterine leiomyosarcoma (485). A retroperitoneal inflammatory leiomyosarcoma was first mistaken for a malignant fibrous histiocytoma (*vide supra*) (486). It is not known if this tumor was EBV-associated. May be all leiomyosarcomas should be submitted to the Chang-Moore digital transcriptome subtraction technology in search for an epigenetically hidden circular EBV genome (as this technology worked for the recognition of HHV8/KSHV, *vide supra*).

In activating the *ras* (Harvey or Kirsten rat sarcoma) proto-oncogenes gammaherpesviruses can induce a cascade of intracellular events, the most prominent being the pre-oncogenic PIK3 'cell survival pathway' (487a).

Viral III. In the chronically inflamed uterine cervix, the high risk papilloma virus deposits its E6 (to target p53) and E7 (to target RB) oncogenes; after neutralizing these tumor suppressor genes, actual activation of oncogenes follows (487b). High risk human papillomavirus, (HPV-16/18), causes squamous cell carcinomas of the uterine cervix, and with or without EBV, is responsible for carcinogenesis in the oral cavity and nasopharynx (487c,488). These are the lymphoepithelioma-like HPV-related head and neck carcinomas (489,490). In North America the incidence of HPV-16⁺EBV⁻ nasopharyngeal carcinomas are increasing (491). High risk HPV-16 shows up in anal warts (491) and in anal squamous cell carcinomas (493).

The target cells of the virus are keratinocytes and other epithelial cells. Against the background of non-specific chronic inflammation (in the uterine cervix, in the nasopharynx, in the ano-rectum), the HPV-16 E6 and E7 oncoproteins heterodimerize with the p53 protein and the RB protein and these complexes are removed by ubiquitination. HPV-16's oncogenes E6 and E7 share a common promoter. The complex formation involves the LXCXE (L, leucine; C, cysteine; E, glutamine and X, any amino acid) motif of E7 fitting into a pocket of the RB protein (494-496). The virally infected cell loses its major propensity toward apoptosis and cell cycle control. Degradation of the regulator of hTERT, nuclear factor binding box 1 (NFX1), removes hTERT repression (human telomerase reverse transcriptase) and thus immortalizes the infected cell. Normally NFX1 promotes the generation of protein p105, an inhibitor of NFκB (497). With degraded NFX1, the p105 protein is not generated; consequentially NFκB levels rise. The virus induces centriole overduplication and the infected cells divide with supernumerary mitotic spindles; consequentially, aneuploidy sets in and the chromosomes become missegregated. HPV-16 activates the polo-like kinase 4 promoter; plk4 mRNAs are overproduced and the cell cycle accelerates its G2 to M progression. Under hypoxic inflammatory conditions, E6 inactivates the human tumor suppressor de-ubiquitinase gene CYLD (cylindromatosis); this act rescues NFκB for unrestricted activity (498-500a). The inflammasome of the uterine cervix is bathed in high levels of the tolerogenic IL-10. It is the peripheral blood mononuclear cells that produce IL-10; the CpG islands of the proximal promoters for IL-10 production in the epithelial cells were silenced by hypermethylation (500b).

There appears to be an abundance of identified and unidentified microRNAs released from the genomes of papillomavirus-infected tumor cells and from the viral genome (501). An outstanding example is miR-200a, which down-regulates oncogenes ZEB1, 2 and TGFβ (*vide supra*). These oncogenes work through the E-cadherin/β-catenin pathway in promoting EMT of the tumor cells, thus initiating metastatic spread. Expression of miR-200a suppresses tumor metastases (502).

The oncoprotein E7 down-regulates the oncosuppressor and cell differentiation inducer miR-203. The target for negative regulation by miR-203 is p63, the level of which gradually drops as stem cells differentiate. Viral oncoprotein E5 lowers miR-203, and raises p63 levels. The cancer cell proliferation inducer miR-146a is active in cervical cancer cells (also active in breast, pancreatic and some prostate cancer cells, as well as in psoriasis). The immunosuppressive miR-146a is strongly up-regulated in cervical carcinoma cells; miR-146a

is up-regulated by oncoprotein E5. From the point of view of inflammatory carcinogenesis, it is important to observe the suppressor of cytokine signaling proteins, SOCS-3: they suppress IL-6 and IFN production. Whereas, miR-203 targets SOCS-3 for negative regulation, thus inducing increased inflammatory responses (503).

Host immunity can eliminate early lesions of cervical carcinogenesis, but the immunity thus gained may be ineffective in protecting against a newly acquired papillomavirus infection (504). High grade cervical dysplasia persists with the continuous expression of the HPV-16 E7 oncoprotein. This oncoprotein overrides the suppressor activity of p21^{cip1} (505). Tumor-infiltrating macrophages are subverted and assume the CD45$^+$, F4/80$^+$ and CD11b$^+$ M2 phenotype of tumor-associated macrophages (TAM). TAM expressed IL-10 and Fox3 and thus antagonized CD8 tumor-immune T cells. CD45$^+$CD11b$^+$Gr1$^+$ myeloid-derived suppressor cells also invaded the tumors. Depletion of TAM with clodronate liposomes restored tumor-immune T cell activity with tumor regression (506). Mice carriers of lung-metastasizing E7$^+$ tumors could be induced into remissions by immunizing them with intra-lymph node injections of an E7 vaccine and treating them with a dsRNA TLR3 ligand (507).

Nitric oxide synthases generate the free radical from L-arginine. The bioreactivity of NO consists of the induction of ss and dsDNA breaks and DNA cross-linkages. In the DNA molecule G:C and T:A transversions occur resulting in the formation of the mutagenic 8-nitroguanine. The wild-type p53 eliminates damaged cells by inducing their apoptotic death. However, when E6 causes the degradation of p53, and E7 blocked the retinoblastoma protein, the mutated virus-carrier cells survive and replicate. Thus an inflammatory condition with the release of free radicals is co-carcinogenic (508a).

About one third (38%) of the inflammasomes of actinic keratosis and the non-melanoma skin cancers (basal cell and squamous cell carcinomas) that follow harbor HPV genomic sequences (by PCR assays), but practically none herpesviral (EBV, CMV) sequences (508b).

Viral IV. Hepatitis B and C viruses with or without alcohol and/or aflatoxin exposure induce hepatocellular carcinoma (HCC), after keeping the liver parenchyma inflamed and becoming cirrhotic for several years (or decades). G1896A and A1762T/G1764 double mutant HBV induces cirrhosis and HCC. Serum HBV DNA levels may clear to the negative stage of HBeAg and HBsAg. G1776A viral genomic mutations favorably prognosticated the achievement of a negative HBeAg status (509,510). The proteomics of infected hepatocytes in patients with hepatitis B surface antigen (SHBs) expression revealed high rate of apoptotic deaths. Apoptosis-susceptibility or resistance was regulated by the following genes: glucose-regulated protein 78 kDa (GRP78), heterogenous nuclear ribonucleoprotein H3, Rho GDP (guanine diphosphate) dissociation inhibitor, cystatin B, far upstream element-binding protein and TNF receptor associated protein 1. The gene GRP78 encoded apoptosis-resistance; siRNA treatment silencing this gene resulted in apoptosis susceptibility. Circulating hepatitis B surface antigen (HBsAG) rendered infected hepatocytes susceptible to apoptosis (511).

The HBV genome is directly oncogenic; it is often compared to the retroviral genome's RNA transcribed into proviral DNA by the viral RT. Like in the case of retroviruses, the HBV genomic DNA also integrates into the host cell's genome. The HBV X gene (Hex) and its oncoprotein eliminate the pro-apoptotic p53 protein, activate methyltransferases to silence more tumor suppressor genes, or gene promoters, by hypermethylation and increase telomerase activity. In summation, it is an anti-apoptosis and anti-senescence agent (512). HBx activates miR-29a, which suppresses PTEN and promotes the migration of transformed liver (hepatocellular carcinoma) cells (513).

Hepatitis C virus (HCV) enters cells through the integral tight junction protein occludin and its membrane-associated MARVEL domain (MAL proteins, myelin and lymphocytes; MAL-related for vesicle trafficking and membrane link) (514). MARVEL-defective cells were non-permissive to HCV entry. The HCV envelope proteins E1 and E2 interact with the phospholipid scramblase 1 securing attachment of the viral particles (515). Only hepatocytes are susceptible to CV entry and its core proteins (Core 3a) interact with host proteins, the heterogenous nuclear ribonucleoprotein H1, nuclear factor 45, and C14 open reading frame 166 (516). These interactions trigger the pre-oncogenic pathways in the infected cells. These processes occur against the background of anti-viral immune reactions in the liver parenchyma, which include oxidative stress and neo-angiogenesis. Generation of iNOS, Cox-2, VEGF, PGE2 and activation of the Akt pathway occur. Administration of Core 3a and Cox-2 specific siRNAs reduced all these reactions and the size of the viral progenies released (517,518). HCV genome encodes p7, a peptide functioning as an ion channel in lipid bilayered membranes. RNA interference (siRNA) inhibits the encoding of HCV envelope proteins E1, 2 and thus reduces intracellular viral replication (519abcd). Chronic HCV infection could culminate into MALT lymphoma with t(14;18) IgH/Bcl-2 translocation (520).

About 55% of the patients with HCV infection treated with pegylated IFNα and ribavirin can achieve sustained viral remissions depending on the viral genotype and the type of the patients' immune response. Of the lympho-cytokine response, steady levels of IL-4 (a Th2-type inducer) and TNFα (a Th1-type inducer) were necessary (521).

Nrf2, the nuclear factor erythroid-2 related factor-2 is activated in response to oxidative stress in HCV-infected cells. MAPK is the activator. Under these circumstances phosphorylated Akt is also activated. Activated Nrf2 and the 'cell survival pathways' overcome BAD (Bcl-2 antagonist of cell death) and prolong the life of HCV-infected cells (522). In HCV-induced liver cirrhosis and HCC, TGFβ induces EMT resulting in invasion and metastasis by the transformed tumor cells (523). Notoriously, NFκB protects HCC from apoptotic death. The protein NEMO (NF essential modulator) activates NFκB; if it is switched off, NFκB remains silent, thus HCCs are allowed to die apoptotic death (524). In patients with advanced pre-cancerous liver cirrhosis, the anti-inflammatory agent colchicine prevented malignant transformation: this occurred in Ciudad Mexico in 9% of colchicine-treated patients versus in 29% of untreated patients (525). Previously, treatment with lamivudine, adefovir, tenofovir protected somewhat patients with hepatitis B from HCC advancement (526). Now, surgically non-resectable HCC is being treated with sorafenib or sunitinib, or with oncolytic virus therapy, i.e., genetically engineered adeno-, herpes-, measles-, myxo-, retrolenti-, vaccinia-, and vesicular stomatitis-

viruses (164,527-531). Sunitinib reduces the number of myeloid suppressor and Treg cells (532). The mechanisms of viral oncolysis directly targeting cancer cells should override any possible adverse effect on inflammatory carcinogenesis.

Bacterial. *Helicobacter pylori* (Hp) is the classical bacterial pathogen that induces severe, host-damaging inflammatory reactions, while depositing its oncogene *cag*A (cytotoxin-associated gene product protein) in epithelial cells of the gastric mucosa, or in lymphocytes invading the lesions. Its pathogenesis generated an excessive literature that was recently and repeatedly reviewed in ref. 62. In a brief summary for a very complex issue (by a clinical oncologist-hematologist-infectious diseases specialist, who has had the opportunity to diagnose and treat patients with *H. pylori*-induced MALT lymphomas): CagA entering lymphocytes and/or gastric mucosal epithelial cells, undergoes phosphorylation, binds Src kinase and *src* homology domain 2-containing tyrosine phosphatase (Rous sarcoma c-*src* proto-oncogene) and activates extracellular signal-regulated kinase (ERK). The MAPK cascade is activated. In lymphocytes, the anti-apoptotic Bcl_{XL} proteins take over. In gastric mucosal cells, *H. pylori* induces hypermethylation of the CpG dinucleotides, and deacetylation of histone tailes, and methylations of selected lysine and arginine groups of histones in gene promoters. The inactivation of the gene for RUNX3 (533) by CpG island hypermethylation provided apoptosis-resistance of the involved cells, mediated by Bcl-2 and Bcl_{XL} overriding the pro-apoptotic BAX and BAK proteins (runt-related transcription factor, B cell lymphoma extra large, Bcl-2-associated X protein, Bcl-2 antagonist killer) MALT lymphomas are originated in the stomach and elsewhere (534,535). Gene translocations characterize MALT lymphoma cells: t(11;18)(q21;q21), t(14;18)(q32;q21) favoring IgH and Bcl-2 and the activation and release of NFκB. Hp-infected macrophages release a proliferation inducing ligand (APRIL) to B cell receptors (536-538).

The epithelial cells assume goblet cell phenotypes ('intestinal metaplasia'). The cytoplasmic β-catenin translocates to the nucleus, where it is to activate some proto-oncogenes (539,540). Several CpG islands are methylated in a reversible fashion: most of the sites (not all of them) get demethylated after the eradication of Hp (541). The WWOX tumor suppressor gene (*vide supra*) is silenced by hypermethylation of its promoter (542). Overriding cell senescence, CagA induces the guanine exchange factor/cMyc/miRNA-p21$^{waf/cip}$ axis for driving the cell cycle toward uncontrolled proliferation and EMT, tantamount to local invasion and distant metastasis formation (535). In Germany, a second Hp protein GroEL emerges independently from CagA, as a major contributor to gastric carcinogenesis (543). Lymphocyte- and granulocyte-monocyte-mediated immune reactions are generated, but fail. Reactive oxygen and nitrogen species rise to induce dsDNA breaks. *H. pylori*-stimulated macrophages in MALT lymphoma release APRIL, the proliferation-inducing ligand (537). Early *H. pylori* invasion is reversible (with specific antibiotic regimens). In a case, *H. pylori* infection was disgnosed and was immediately treated, while lymph node biopsy results were not immediately available. Treatment for *H. pylori* infection resulted in rapid regression of lymphadenopathy. Thereafter the lymph node biopsies revealed Burkitt's-like lymphoma EBV-negative with c-Myc rearrangement, but without Bcl-2 translocation (544).

Hungarian clinicians are very interested in those enzyme inhibitors (targeting urease, carbonic anhydrase, γ-glutamyl transpeptidase, efflux pump inhibitors) that may inhibit the growth of chlarythromycin-resistant strains of Hp (545).

Genitourinary parasites. *Schistosoma haematobium* induces squamous cell carcinoma of the urinary bladder in Central and North Africa (Burkina Faso; Cameroon; Egypt, Entebbe, at Lake Victoria, Uganda; Msambweni, Kenya; Southwestern Morocco, Lake Malawi, Nyasa/Niassa, Mozambique and Tanzania; Erinia River, Osun, Nigeria; Niger; Lusaka province, Zambia; lakes and Limpopo River, Zimbabwe). The intermediate host is the snail sp *Bulinus* (especially *B. truncates/truncatus*). However, it was in Brazil, where the hemocytes of the snail sp *Biomphalaria* were found to be self-protective against *S. mansoni*. The snail hemolyph contains amoebocytes and haemocytes; the haemocytes are granulocytes and hyalinocytes. The granulocytes move on psedopods, phagocytose and encapsulate the parasites (546). Eli Metchnikov (ИЛЬЯ ИЛЬИЧ МЕЧНИКОВ 1845-1916) observed the phenomenon of phagocytosis in the belly of *Daphnia pulex*, whose entire genome has just now been sequenced in full. The innate immune faculties of the snail offer better protection against the cercaria (547), than the united innate and adaptive immune faculties of the human host. The snail phagocytes generate nitrite oxide to kill the parasites. In the human host, tumor cell genomics give no clear explanation of the pathognesis. Genomics (including the mt genome) of the parasites revealed the lines of their phylogenesis, but so far gave little information as to their ability of evading the infested host's defenses (548,549). However, an extraordinary study on the snails' innate immunity as it is activated against the trematodes, revealed that their thioester-containing protein (TEP) regulates the phagocytosis and encapsulation of the parasites. The fibrinogen-related proteins (FREPs) in a specific and variable manner react with polymorphic mucins of the parasites. These reactions are between diversified immune receptors of the host, and antigenic variants of the parasite (550). In the human host, the tumor suppressor gene p53 may or may not be downregulated, but the anti-apoptotic Bcl-2 gene is activated (551). Only the mucinous and signet ring adenocarcinomas expressed intense c-Myc (552). The RB gene was occasionally suppressed; p53 mutations occurred in 57% of the tumors. Ras gene point mutations, EGFR c-Erb2 amplifications occurred irregularly (553). The detectable genomic changes (p53, H-ras, VEGF) could not be used as prognostic factors as to the outcome of the disease (554). However, p53 mutation and high Ki-67 expression indicated advanced disease and poor prognosis (555). Human cancer cells, especially those of colon carcinoma, overexpress the highly conserved oncofetal antigens TA1/E16 (tumor-associated, embryonic day 16 lymphocyte activating). Protein homologues of these antigens are expressed in schistosoma species (*S. mansoni*) (556), and as such, they may act as oncogenes in human cancers.

Polo-like kinases (Plk-1-5) encode centrosome spindle formatting proteins in schistosoma and in cancer cells. The patented drug Bl2536 inhibits mitoses in schistosoma and in cancer cells (557).

Opisthorchis viverrini, and *Clonorchis sinensis*, the liver flukes, induce cholangiocarcinoma of the bile ducts. In the tumor cells Ski/SnoN oncoproteins are highly overexpressed

(Sloan-Kettering Institute). These are avian retrovirus-related oncoproteins discovered at the Sloan-Kettering Institute, New York. Proto-oncogene v-*ski* was captured by an avian erythro-leukemia retrovirus SKI-T (c-*ski* → v-*ski*). The human c-*ski* locus maps to 1q22-24. Oncoproteins c-Ski/SnoN (Ski novel protein) are overexpressed in cholangiocarcinoma with or without induction by *O. viverrini*. SnoN binds the Smad complex and repress TGFβ's inhibitory effect on cell proliferation, thus acting as an oncogene. SnoN binds the promyelocytic leukemia (PML) protein and they thus stabilize p53; the cell undergoes senescence and apoptosis. SnoN acted as an anti-oncogene (EMBO J 2889). In cholangiocarcinoma cells, the retinoblastoma (Rb) and p16(INK4) proteins are reduced. Cyclin D1, CDK4 and Smad4 are up-regulated (inhibitor of CDK4, cyclin-dependent kinase; mothers against decapentaplegic, from drosophila; decapentaplegic = TGFβ ligand). Oncoprotein c-Ski suppresses TGFβR, as its direct antagonist. Active TGFβ antagonizes c-Ski by suppressing its neoangiogenic and metastatic potentials. The negative c-Myc regulator tristetrapolin (TTP) is disabled by a CpG site methylation, thus liberating c-Myc for the suppression of the anti-proliferative effect of TGFβ (558-566).

Are the notoriously present latent polyomaviruses JC and BK contributory to carcinogenesis in the GU tract? Extending the question to SV40 simian polyomavirus, that was present in some live attenuated poliomyelitis vaccines, and to the Merkel cell carcinoma polyomavirus, these agents are highly suspect contributors to some rare human neuroectodermal cancers expressing the T oncoprotein and/or integrated viral genomic sequences in the tumor cells' genome. Inflammatory monocytes serve as a reservoir for the Merkel cell polyomavirus (567-572).

5. Mechanisms of inflammatory carcinogenesis

Proteomics. Granule-loaded eosinophil granulocytes are expected to exert complex anti-tumor effects wihin inflammasomes (*vide supra*). In Hodgkin's granulomas the eosinophils fail to subdue the Reed-Sternberg cell (Fig. 2). The eosinophil granulocytes themselves may succumb to malignant transformation in the form of various hypereosinophilic syndromes including eosinophilic leukemia. The fusion inducing protein/oncogene includes the platelet-derived growth factor receptor α gene (FIP/FDGFR), susceptible to inhibition by imatinib mesylate or dasatinib. Inflammatory defensive cells, be monocytes, granulocytes, lymphoid cells (lymphocytes and NK cells) or mast cells, do readily succumb to malignant transformation. TAMs are often subverted supporters of growth factors to the tumor. Immature dendritic cells (DCs) are often tolerogenic. The presence of CD123+ plasmacytoid DCs in breast cancer tissue is associated with poor prognosis (13).

Genetic polymorphisms (single nucleotide polymorphisms, SNP) may bring out the unexpected: a defensive immune reaction may be the inducer of malignant tranformation in these individuals. SNP of the TLR4 or some of the 'inflammatory genes' increases the risk of high grade prostate cancers. Pro-inflammatory IL-1 gene cluster polymorphism increases the risk of gastric cancer induction in the *H. pylori*-infected organ (*vide supra*). When TLR4 recognizes LPS endotoxin, it signals through MyD88/IL-1 to induce NFκB and the MAPK pathway. Polymorphism of the TLR4 gene may result in defec-

tive signaling, lack of defensive reactions and consequentially severe direct tissue damage by the endotoxin (13).

Of damage-associated molecular pattern (DAMP) molecules, high mobility group proteins A and B emerge (HMGAB), as they are released from necrotic cells. The cognate receptors of HMBAB proteins are the RAGE (receptors for advanced glycation end products, glycation, non-enzymatic glycolyzation), or TLR2, TLR4. These receptors generate NFκB, E-selectins and insulin-like growth factor and/or its receptor, IGF-R (selectins are ligands to sialylated cell surface carbohydrates) (13).

How could defensive inflammatory reactions of a host derailed toward carcinogenesis? The promotion of the HER2/neu oncogene by Freund's adjuvant settled the issue (573). Dormant oncogenes are awakened and activated, when the host mobilizes inflammatory reactions. The importance of chronic inflammatory processes in carcinogenesis is best proven by the anti-oncogenic efficacy of anti-inflammatory agents. The most efficient anti-inflammatory and oncogenesis inhibitory agents are ethyl pyruvate, non-steroidal anti-inflammatory drugs (acetyl salicylic acid, ibuprofen), prostaglandin- and COX2-inhibitors (celecoxib) (13).

The human nitric oxide synthase gene is up-regulated by the Wnt/β-catenin/Tcf4 signaling (T cell factor/lymphoid enhancer factor). TNFα, IL-1β and IFNγ induce nitric oxide expression (hiNOS) by acting on the NOS gene promoter. NFκB is suppressed by β-catenin. The summation of these reactions is a decrease of hiNOS production in colon cancer and hepatocellular cancer cell lines (574).

Autophagy. Reduced HMG proteins induce mitochondrial superoxide production promoting autophagic cells. Other inducers of autophagy are perifosine (an mTOR inhibitor), and TGFβ (a multifunctional cytokine) (575,576). In autophagic cells, induced by autophagy genes, the cell survival pathway PI3K and the pro-apoptotic beclin (the mammalian ortholog of yeast autophagy gene, *atg*) compete; Bcl-2/Bcl$_{XL}$ antagonize beclin (577). Autophagic tumor cells may recover as progressive tumors; this can be inhibited by hydroxychloroquine (578). Autophagy may protect tumor cell during genotoxic and metabolic stress. However, resveratrol and curcumin may induce tumor cell death in autophagy and in mitotic catastrophe (579-581). The mitochondrial alternating reading frame, p14^{ARF} exerts anti-tumor effects by antagonizing MDM2, thus protecting p53, and suppressing c-*myc*/MYC. In autophagic cells, p14^{ARF} removes the Beclin/Bcl$_{XL}$ complex and suppresses tumor cell recovery from autophagy (582). Inflammatory events in the tumor environment may induce autophagy of tumor cells as a stress adaptation response (583ab).

Autoimmunity. The epigenomics of EBV (474,584,585), and reactivated endogenous retroviruses definitely are major contributors to the etiology of autoimmunity, especially in lupus erythematosus and multiple sclerosis (reviewed in ref. 178,474,586).

While the omnipresent cytoplasmic filamentous structures were not unenveloped myxo-, or retroviral strands (587ab,588), but products of the endoplasmic reticulum in response to IFNαβ oversecretion, serological and biochemical evidence for a herpesvirus (EBV) triggering the maturation of endogenous

retrovirus(es) is becoming steadily more convincing throughout of the passing decades (62,152,474).

One would expect that the chronic (but self-directed) immune reactions would increase the incidence of malignant tumors, especially those of the lymphatic system. Increased lymphomagenesis in patients with autoimmune diseases (lupus) is well confirmed. The incidence of parotid gland marginal zone lymphoma in patients with Sjøgren's syndrome is 1000-fold increased. In SLE, lymphomagenesis is minimally (3-fold) increased (589). Further, it is suspected, but not proven, that EBV in the background, and sporadic buddings of endogenous retroviruses in the lymphoma cells in the foreground, are the etiological agents (178). Unexpectedly, there is lower incidence of adenocarcinomas (breast, colon, prostate) against the background of a *bona fide* autoimmune disease, treated or untreated (590,591). The German Cancer Research Center in Heidelberg suggests that the natural risk for cancers in autoimmune diseases is increased, but is artificially reduced by suppressing the inflammatory component of cancer induction by anti-inflammatory medications (592). MicroRNA-155 emerges as one of the master regulators of immune cell generation, as it has the ability to target mRNAs of a wide variety of the cellular immune system. Should a lymphoid cell population turn malignant, miR-155 may be able to suppress its mRNAs (593).

The IL-17$^+$CD4$^+$Th17 lymphocytes are known to mediate autoimmune reactions. A stimulatory role to anti-tumor immune CD8$^+$ T cells of a Th17$^+$ lymphocyte subpopulation was recognized; chemokines CCL2 and CCL20 and IL-2 mobilized this population of Th17 lymphocytes, which did not have the ability to directly kill tumor cells (594). An IL-17$^+$CD4$^+$FoxP3$^+$ regulatory Th17 cell population forms the minority of Treg cells. This population of Th17 cells derived from CCR6$^+$ memory T cells under the effect of myeloid antigen-presenting cells, IL-2 and TGFβ. In the colon, the CD4$^+$Fox3P$^+$Th17 lymphocyte population suppressed CD8$^+$ T cells, and induced inflammatory cytokines. The Th17reg cells promote ulcerative colitis and thus colon carcinogenesis (595).

Reactive oxygen species and related genotoxic events. Positive comments on inflammatory carcinogenesis based on dsDNA damage (breaks, mutations) by reactive oxygen and nitrogen species abound in the literature (596-598). Followers of Professore Flaviano Magrassi, distinguished member of the 'Accademia Nazionale dei Lincei', from Naples, Italy, state 'A mutated cell is a *sine qua non* for carcinogenesis' (596). Hypoxia, DNA damage and genome instability; DNA breaks misrepaired (in the form of fusions of distant genes); aging and cancer; the necessity of G protein-coupled receptor for p53-dependent cell survival in response to genotoxic stress; nicotinamide phosphoriboyltransferase: a molecular link between metabolism, inflammation and cancer; aldehyde dehydrogenase-expressing colon stem cells contributing to tumorigenesis in the transition from colitis to cancer; high mobility group A1 gene: transforming inflammatory signals into cancer; oxidative stressing in prostate cancer is required for aggressive phenotype; role of IAPs in NFκB activation by genotoxic stresses; mitochondrial dysfunction and reactive oxygen species imbalance promote breast cancer motility through CXCL14; tyrosine kinase c-Src in the regulation of reactive oxygen species generation; role of mismatch repair in the control of oxidative DNA damage;

genetic instability and tumorigenesis; induction of epigenetic alterations by chronic inflammation and its significance in carcinogenesis, are the long list of topics recommended for review from the Epub service. Indeed, a high innate production of pro-inflammatory cytokines was a signal for increased risk for death from cancer (599).

Oxidative DNA damage occurs consequentially to 'leaks' from electron transport chains. Leak electrons acting with oxygen produce superoxides often released in bursts. Certain enzymes also generate superoxides released in bursts. This is the established practice of phagocytic cells for the destruction of pathogens. Peroxisomes practice normal oxidative metabolism. The unintentional oxidative damage to DNA is caused by the highly reactive hydroxyl radicals abstracting H atoms from the methyl groups (CH$_3$) of thymine and from the C-H bonds of 2'-deoxyribose. Additions to the C5-C6 double bond of pyrimidines transforms these into C5-OH and C6-OH adduct radicals. H atom abstraction from thymine forms an allyl radical. The C5-OH adduct radicals are reducers, and the C6-OH adduct radicals are oxidizers. Addition of oxygen to C5-OH adduct radicals yield C5-OH-6-peroxyl radicals. C5-OH-6-peroxyl radicals eliminate O$_2$··; after reaction with water, thymine and cytosine glycols are formed. Allyl radicals reacting with oxygen form 5-hydroxymethyluracil and 5-formyluracil. Thymine peroxyl radicals are reduced to hydroxyhydroperoxides decomposing into thymine glycol, and 5-hydroxyl- and 5-formyluracyls and hydroxyl-methylhydantoin. In certain early stages, oxidative DNA damage can be repaired. Genome repair begins with the enzymatic reactions: glycolases removing single lesions, or enzymes excising nucleotides. These are highly specific processes, like the removal of purin-derived, or pyrimidine-derived oxidative lesions. The repair may be defective, but the DNA remains functional. For example, deamination of cytosine to uracil is a pro-mutagenic mistake (600). The glutathione peroxidase gene (GPX1) in the short arm of chromosome 3 frequently suffers loss of heterozygosity (LOH), thus producing a defective enzyme, the gene product protein peroxide scavenging enzyme (600).

These events occur when the repair genes suffered SNP (*vide supra*). In response, mammalian cells express stress-induced genes encoding antioxidant reactions. However, further reactions along these lines leave the DNA molecule either mutated or non-functional. The scientific community hypothesizes that if the mutated cells are not eliminated by the 'guardian of the genome', the WTp53 pro-apoptotic machinery, mismatched repairs and gene fusions may resurrect the damaged cell in a shape and condition not fit into the orderly operation of a multicellular organisms, as if the resurrected cell would not fit into an organized cell community, but could live as a unicellular organism on its own. For example in a tissue culture vessel nourished and cleansed. Under these circumstances it would prove itself to be exempt of senescence and natural death. Its DNA would dictate incessant cell divisions 'forever'. This author, growing EBV$^+$ human lymphoblasts in suspension cultures and sarcoma and melanoma cells in solid cultures for over a decade, wrote in 1976 (321,601a): 'Could the cancer cell be viewed as an individual that extricated itself from boundaries exposed (imposed) on it by 500 millions years (3 billion) of evolution and recaptured the immortality of unicellular organisms that existed before the social order of cell communities was estab-

lished? Certainly, some cell cultures of mammals, including man, create the impression of immortality of archaic unicellular life forms (i.e., lymphoblastic cells grown in suspension culture as long as nutrients are provided and metabolic waste is removed)' (601a). However, if the resurrected cell remains in its cell community, it may be attacked and killed. It may be able to evade such attacks and continue to replicate and eventually consume its host, as if it were an alien invader (601a).

'Demonstrating a link between defects in repair of oxidative DNA damage and a propensity for disease has not been easy'. Carcinogenesis probably requires combined gene mutations or knock-outs. 'The mere presence of damage is not proof of a causative link' (600), a scientifically justified most cautious comment in 2003; by 2010 the evidence for a positive relationship between inflammatory processes and carcinogenesis has reached an overwhelming volume and quality (599).

The empress (RNA) and the emperor (DNA) of all molecules. The ancient RNA/DNA interactions continue in the most complex intracellular environments. The position of the stem cell gene Sox2 residing embedded in a long non-coding RNA strand (359), strongly suggests that such constellations might have already been formed in the precellular era on Earth. The microRNAs retain the power over DNA as they are capable of silencing the mRNAs of DNA-derivation. Actually, the microRNAs cooperate with the DNA, when the stem cell- or somatic cell-serving DNA genome transforms itself into a set of multiple oncogenes, thus preventing the cells' senescence and death. It may appear as if the microRNAs dictated the reversal of the cell-serving DNA into its primordial 'immortal' format (*vide infra*). The stem cells may rest, self-renew, yield daughter cells for specific differentiation in the form of functional somatic cells, or transform toward immortalized cell populations, whereby the DNA genome undergoes ds breaks; misrepaired, the dsDNA breaks result in gene fusions and oncogene formations, while genes inhibitory to this process (the 'tumor suppressor genes') are deleted. Inflammatory processes frequently signal the stem cell (or the differentiated somatic cell) toward the latter pathway. It appears as if microRNAs guide the DNA toward which way to go. Thus inflammatory reactions indirectly through miR-mediation penetrate the epigenome and act through its modification. A scholarly review spreads the word in Hungarian (so convincingly, as if the crosstalk between RNA and DNA actually went on in Hungarian) (601b). Indeed, the ancient RNA/DNA crosstalk should be understood in all languages. It is spelling out the verdict of life or death for the cell, from the time on, since cells lived on Earth. The extraordinary versatility of the DNA in its transformation into sets of oncogenes and its interaction with the epigenome in the process was well recognized even before the discovery of the microRNAs (602).

The question arises if it is not so, that hyperthermia (HSF), hypoxia (HIF), reactive oxygen/nitrogen species (ROS, iNOS) and stress, and showers of inflammatory cytokines release their danger signaling to the RNA/DNA complex. The somatic cell-serving DNA in multicellular organisms accepted senescence and death, but retained suppressed but preserved, its primordial faculties of independence and 'immortality' in the germ cells and in the stem cells. The haploid germ cells in their unisons become differentiating somatic cells. However, the self-renewing stem cells, instead of the route to differentiation, may choose a reversal toward a primordial stage of life: restoring the ancient DNA and the ways it existed under precellular conditions intimately reacting with RNA and with 'amorphous proteins', as amino acid chains 'self-replicating' (603,604). In the first cellular life forms, DNA was highly resistant to physicochemical damage and voraciously accepting for fusion and recombination alien genomic sequences (62). Upon the encounter of amorphous proteins and naked DNA, the proteins engulf the DNA and DNA strands penetrate to the helices of the proteins, while the proteins undergo subtle morphological changes of their nanoparticulate architecture (604). Innumerable such newly formed structures may exist in nature without being able to enter cells for replications, inasmuch as the natural proteins can not serve as specific ligands to any cell receptors (whereas, the proteins generated in the Domingo-Espin laboratory were actually encoded by borrowed viral genes from the foot and mouth virus and from the SV40 virus, and thus have become 'artificial viruses' able to react with cell and nuclear membrane receptors and transgress them) (604). In contrast, the natutally formed entities may show up in the metagenomic samples (in a mixture with regular incomplete virions), as the 'gene transfer agents' of Kristensen *et al* (605), or among the structures considered to form a 'fourth domain of life' on Earth (606).

The spheroplasts of a crenarchaeota and a prokaryota might have been fused by a fusogenic phage of an ancestral mycoplasma (like that of the *Acheloplasma* sp) to form the first eukaryotic cells (an experiment of Nature that could be repeated in the lab today) (607). Since their origin by cell fusion, eukaryotic cells continue to readily communicate through cell fusions in physiological or oncogenic terms; all oncogenic viruses are able to fuse cells (62,608,609). Lymphoma cells naturally fused with specific antibody-producer plasma cells (referred later to as 'natural hybridomas') discovered in mice in the late-1960's are presumed to exist in human patients (62,225,610-614). In the first unicellular nucleated eukaryotes, with or without the acquisition of mitochondria or chloroplasts, the RNA/DNA complex maintained its superiority over all other molecules, either within the cell, or outside the cell, as phages converted into RNA ('the burst' of picornaviruses) (615), and into DNA eukaryotic viruses (616). Those sophisticated cells divided before senescence and death; natural death was not encrypted in their DNA genomes. In adverse circumstances, the most versatile ancient DNA transformed them into morphological and physiological entities grossly different from their basic original life forms: as if into a different (from an a-flagellate to a flagellate) species. The *Naegleria* DNA still practices such transformations of its host (617,618). Later, in the unicellular parasite *Theileria* under immunological attack in an invaded bovine host, the most versatile theileria DNA encodes an elaborate physiology for the parasite to evade that immunological attack from its host (619). In the theileria-induced fatal lymphoproliferative disease, the East Coast fever, the parasite induces NFκB to secure apoptosis-free state of the schizont-infected lymphocytes. Theileria-infected macrophages bring into existence an autocrine loop for TGFβ2 and induce MMP9 for their survival and invasiveness (620,621), thus using the same molecular mechanisms cancer cells utilize for their survival and invasiveness. In the glioblastoma cell, the DNA can switch from the anaerobic glycolysis to oxidative phosphorylation and metabolism (622).

The Namalwa Burkitt's lymphoma cell DNA under attack with heavy irradiation, suffers severe ds breaks. The γH2AX (ataxia) histone detects an extraordinarily high incidence of these ds breaks. However, the oncogenic DNA (with the help of repair enzymes like the recombinase Rad51, forming nucleoprotein complexes from ss/ds broken DNA sequences) recovers from the 'mitotic catastrophe' (623). In the enzyme-free (except for the ribozymes) pre-cellular RNA/DNA world, ss or dsRNA/DNA breaks might have been repaired telomere-free by end-to-end seals (which are chromosome fusions in the celluler world) (624).

The existence of viral genes related to RNA/DNA replication, but not shared with cellular genes (the 'viral hallmark genes' of Koonin *et al*, *vide infra*) strongly suggests that the origin of these genes predates the appearance of protocells (625). For self-replicating macromolecules in hypercycles (a symbiosis of molecules self-replicating in hypercycles, Ghadiri *et al*, *vide infra*), the Eigen's error catastrophe phase transited into a thermodynamic phase governing templated RNA/DNA synthesis (626).

Following the ideas of old-time astute observers, Arguello proposes that the cancer cell is the result of an 'atavistic metamorphosis' (627a). Duesberg *et al* (627b) consider the cancer cell to be the product of a trans-speciation process.

The oncogenic DNA bioengineers the neoplastic cell as its ancestors could (and still do) bioengineer the naegleria cell, while it remains close to indestructible, as its predecessor, the primordial DNA, must have been (628). Are oncogenes representing a reversal of the cell-serving DNA to its primordial format? Is the multiply fused and most powerful oncogenic DNA a replica of the primordial DNA? Is it not so, that the malady that we diagnose as 'cancer', is the expression of an inherent fundamental attribute of the DNA, its reversal from the differentiated to the native undifferentiated format in order to sustain life under any conditions and in any shape (628)? Were it not our killer, scientists would admire the cancer cell and its DNA 'oncogenes' as the ultimate achievement of bioengineering.

A 'precellular virus world' and a 'primordial gene pool' could have formed on Earth (629). That world can not only be imagined, but could possibly be duplicated in the laboratory. How the naked DNAs interacted with amorphous amino acid clusters (603,604), hypercycling RNAs in the hydrothermal vents at the bottom of the oceans (and in their laboratory reactors) (630), the catalytic hammerhead ribozymes (631), and the circular self-replicating ('rolling circle') viroid RNAs (preserved from the pre-cellular world in extant plant and mammalian cells, the hepatitis δ viroid, some with a tandemly repeated homologous DNA attached) (632-635)? In order to envision these interactions in a most hostile precellular environment without potent protein enzymes, that were not being able to form without cellular ribosomes and without a genetic code, both advanced knowledge in proteomics and genomics, and a great deal of imagination, are required. This author for one, subscribes with gratitude the review, Professor W. Ford Doolittle (Dalhouise University, Halifax, Nova Scotia, Canada) rendered, to Koonin *et al*: 'Virus-like entities surely predated the appearance of modern cells…Evolutionary scenarios are an artform. They usefully exercise the brain…They do not have to be true! I do not disfavor the publication…' (629).

Acknowledgements

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