NF-κB, inflammation and pancreatic carcinogenesis: NF-κB as a chemoprevention target (Review)

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Abstract. Pancreatic cancer is the most deadly of all gastrointestinal malignancies with near zero five-year survival. This review summarizes our understanding of the potentially important role of inflammation in cancer in general and pancreatic cancer in particular. Nuclear factor κB (NF-κB), a mediator of inflammatory responses, plays a significant role in carcinogenesis and is now emerging as a link between inflammation and cancer. NF-κB is activated in over two thirds of human pancreatic cancers; participates in early events of pancreatic carcinogenesis through its interactions with signaling pathways; and suppression of its activation restores pancreatic cell kinetics, mainly normalizing the suppressed apoptosis of pancreatic cancer. NF-κB is an excellent target for chemoprevention and its modulation for pancreatic cancer prevention appears promising. The next few years will likely expand our understanding of NF-κB biology; solidify NF-κB's role as a major link between chronic inflammation and pancreatic carcinogenesis; and witness the development of NF-κB-based approaches to pancreatic cancer prevention.

Contents

1. Introduction

Each year more than 29,000 Americans are diagnosed with pancreatic cancer. Six percent of all cancer deaths in women and 5% in men are due to pancreatic cancer, making it the fourth leading cause of cancer deaths in the US. Pancreatic cancer is referred to as 'the dismal disease' because of its aggressive nature. Early diagnosis is difficult and by the time the disease is recognized clinically it is usually too late to help the patient significantly. Pancreatic cancer is usually fatal within 6 months (1,2). The lack of a successful treatment for this disease reflects to a large extent our limited understanding of its etiology and molecular pathogenesis and the paucity of methods for its early detection.

The disappointing performance of current treatment modalities necessitates the development of effective chemoprevention strategies against pancreatic cancer. To achieve this goal, it is crucial to understand the molecular mechanisms underlying pancreatic carcinogenesis. In the last few years, inflammation has emerged as an important factor in pancreatic carcinogenesis (3). The exact link between chronic inflammation and carcinogenesis, however, remains unclear. Nuclear factor κB (NF-κB), a mediator of the inflammatory pathway, appears to be crucially involved in carcinogenesis (4-18). This review examines the role of NF-κB in carcinogenesis with emphasis on pancreatic cancer; discusses its role as the link between inflammation and pancreatic cancer; and assesses data suggesting that pancreatic cancer may be prevented though modulation of NF-κB signaling.

2. A brief overview of NF-κB

NF-κB is a transcription factor discovered by Sen and Baltimore in 1986 in the nuclei of mature B lymphocytes, where it bound specifically to a decameric sequence in the enhancer region of the κ light chain (19). It quickly became apparent that NF-κB is present in virtually every cell. This transcription factor has attracted wide interest for three reasons. First, it is activated by a variety of stimuli, most, if not all, of them biologically relevant. They include, among others, reactive oxygen intermediates, hypoxia/anoxia, hyperoxia, cytokines, protein kinase C activators, mitogen-activated protein kinase activators, bacterial or viral products, dsRNA and UV radiation. Second, NF-κB controls over 150 genes and several biological responses, including innate and adaptive immune responses, stress responses, cell survival and proliferation. Third, there is considerable evidence that NF-κB is involved in many human diseases, including cancer (20). Recent studies indicate that NF-κB plays a key role in pancreatic carcinogenesis (3,21-23).

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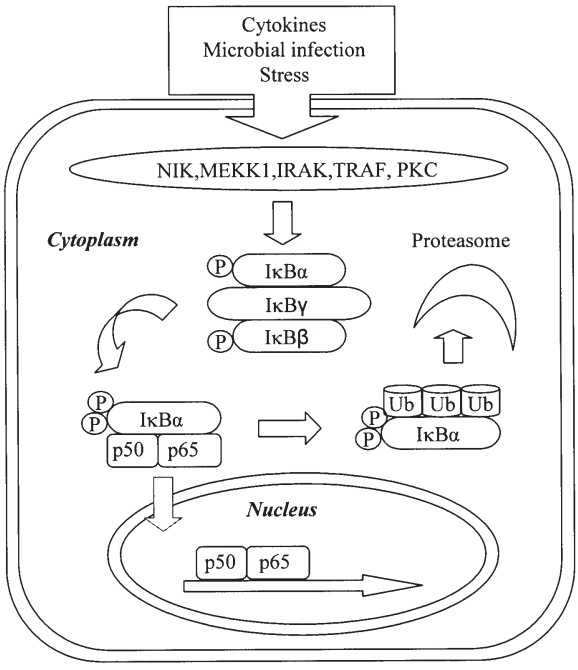

Figure 1. The canonical pathway of NF-κB activation. In response to various stimuli, IκB is phosphorylated and degraded by the proteasome, thus liberating the NF-κB dimer (here depicted in its most frequent combination, p50/p65), which subsequently translocates to the nucleus where it acts as a transcription factor, influencing the expression of over 150 genes and through them several biological responses. Non-canonical pathways, not shown here, have also been described (reviewed in ref. 10).

Table I. Chronic inflammation and associated cancers [modified from Li *et al* (11)].

Chronic inflammation	Associated neoplasm
Chronic bronchitis	Lung carcinoma
Gastritis	Gastric adenocarcinoma
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical carcinoma
Warts	Non-melanoma skin carcinoma
Inflammatory bowel disease (Crohn's disease, chronic ulcerative colitis)	Colorectal cancer
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma
Hepatitis	Hepatocellular carcinoma
Mononucleosis	B-cell non-Hodgkin's lymphoma, Burkitt's lymphoma, Hodgkin's disease
Chronic cholecystitis	Gallbladder cancer
Gingivitis, lichen planus	Oral squamous cell carcinoma

The functional NF-κB protein is composed of two subunits, usually the heterodimer of p65/RelA and p50 (24) (Fig. 1). The NF-κB dimer is sequestered in an inactive form in the cytosol where it is bound to a member of the IκB family of inhibitory proteins: IκBα, IκBß, IκBε, IκBγ, Bcl-3, p100 and p105; of these, IκBα and IκBß are the most abundant (25). Both of them have two N-terminal serine residues that can be phosphorylated by IκB kinase in response to diverse stimuli including cytokines, viral and bacterial pathogens, and stress-inducing agents. The phosphorylated IκBs are then ubiquitinated and proteolytically degraded. The degradation of IκBs unmasks the nuclear localization signals on the NF-κB subunits, permitting NF-κB to translocate to the nucleus, where it binds to specific DNA sequences in the promoter or enhancer regions of target genes, initiating gene expression (3,5,9-11,21).

3. Inflammation and cancer

The relationship between inflammation and the development of cancer has been recognized for nearly two centuries. Hawkins made in 1835 the first relevant clinical observation, reporting that squamous cell carcinoma can be a long-term sequela of chronic osteomyelitis in the overlying skin (26). In 1863, Rudolf Virchow observed leukocytes in neoplastic tissue and suggested that this reflected the origin of cancer at sites of chronic inflammation (27). In 1891, Westphal reported dense areas of mast cells at the periphery of tumors (28).

The inflammatory component of a developing neoplasm includes a diverse leukocyte population, e.g., macrophages, neutrophils, eosinophils, and mast cells, all of which are variably loaded with an assorted array of biologically active mediators (29). According to a plausible hypothesis, inflammatory cells are involved in the neoplastic process as part of the normal host response, when malignancies arise from areas of infection and inflammation (17). Approximately 15% of malignancies worldwide can be attributed specifically to chronic infections yielding a global total of 1.2 million cases per year (30). Prominent among the mechanisms by which infectious agents may induce carcinogenesis is the production of a state of chronic inflammation.

The most compelling evidence for the apparent link between inflammation and cancer comes perhaps from the discovery that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) decreases cancer risk. A large body of epidemiological data has documented that NSAIDs prevent several cancers, including colon, gastric, estrogen receptor positive breast cancer and perhaps pancreatic and ovarian cancers (31). For colon cancer, recent interventional studies have provided formal proof for cancer prevention by aspirin (32); for the rest the strength of the evidence is variable.

Several cancers have been linked to inflammatory origins, as shown in Table I. One of the best-characterized examples of inflammation leading to cancer is the development of squamous cell carcinoma at the site of burned skin (33). The tumor arises from the inflamed epidermis providing a clear correlation between inflammation and malignancy. There are also additional examples of cancers developing on a clinically well recognized background of inflammation. They include: a) the development of colorectal cancer in patients with inflammatory bowel disease; it is now clear that its mechanism is related to inflammation and is distinct form that of sporadic colon cancer (34,35), and b) the development of gastric cancer secondary to infection with *Helicobacter pylori* (36).

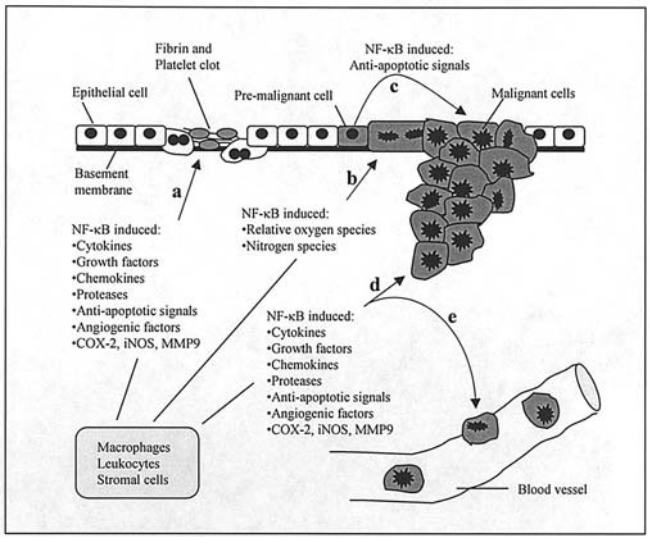

Figure 2. The role of NF-κB in inflammation and inflammation-associated cancer. (a), Leukocytes and stromal cells secrete a plethora of proinflammatory proteins during inflammation. (b), Proinflammatory factors in the micro-environment of the dormant pre-malignant cells lead to the accumulation of DNA damage, which, in turn, causes these cells to become malignant. (c). Activation of NF-κB in pre-malignant cells induces anti-apoptotic signals, which prevent apoptosis and enhance their proliferation. (d and e), Leukocytes or stromal cells secret proinflammatory proteins in the chronically inflamed microenvironment, which stimulate tumor progression and metastasis. All these signals are regulated by the classical NF-κB pathway, shown in Fig. 1, underscoring the potential of NF-κB inhibition in the prevention and perhaps treatment of inflammation-associated cancer.

Despite extensive efforts in the last few years, the nature of the link between chronic inflammation and carcinogenesis remains unclear. Kinzler and Vogelstein, in their cataloguing of the potential mechanisms of colon cancer development, have included inflammation as one of four mechanisms under the descriptive term 'landscaper defects' (37). This concept is exemplified by patients with juvenile polyposis syndrome or ulcerative colitis, who develop hamartomatous polyps in which the proliferating defective population of cells appears to be derived from the stroma. Consequently, the epithelial cells associated with the polyps are more likely to undergo neoplastic transformation, as a result of an abnormal microenvironment. Likewise, the initially normal epithelial cells associated with the inflammatory process of ulcerative colitis are at increased risk of neoplastic transformation (38,39). In this context, it is important to note that recently the *ras* pathway was shown to stimulate IL-8 production in tumors, which, in turn, recruits more inflammatory cells to the site of inflammation and therefore contributes to inflammation-associated tumorigenesis (40,41) (Fig. 2). Of interest, the inflammatory environment itself might also provide anti-apoptotic stimuli to pre-malignant cells. Although proinflammatory stimuli are intended to initiate an immune response, they can also stimulate stromal fibroblasts to produce growth factors, initiate malignant cell growth, inhibit apoptosis, inhibit cytotoxic T-lymphocyte activity, promote angiogenesis, facilitate metastasis and enhance tumor-associated macrophage infiltration (29). Furthermore, tumor-associated macrophages are 're-educated' by tumor cells to produce pro-tumorigenic factors, such as angiogenic factors, matrix metalloproteinases and reactive oxygen and nitrogen species, which increase DNA damage (14).

An inflammatory site is characterized by the local expression of proinflammatory cytokines, chemokines and adhesion molecules, which regulate the sequential recruitment of leukocytes and stimulate fibroblasts and endothelial cells to divide and produce components for tissue remodeling and neovascularization (7,9,10,29,42). The innate immune response is activated by a range of stimuli, including pathogens, stress signals and proinflammatory cytokines, e.g., interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α).

The NF-κB pathway regulates the proinflammatory response. Activation of NF-κB involves the translocation of the active dimer (often p65-p50) to the nucleus where it activates transcription of proinflammatory cytokines, adhesion molecules, chemokines, growth factors, anti-apoptotic genes and cyclin D1 (43-47). In addition, NF-κB induces other proteins such as nitric oxide synthase and cyclooxygenase-2 (COX-2), both critical mediators of the inflammatory process (48). This sequence of events, detailed later on for the specific case of pancreatic cancer, highlights NF-κB as a molecular link between the activation of inflammatory pathways and loss of normal cell cycle regulation in cancer.

It should be noted that there may be exceptions to this straightforward association between inflammation and cancer. The evidence comes from certain types of inflammatory processes in skin, which may also serve a tumor suppressor function (7). Thus, inflammatory reactions that activate signaling pathways such as NF-κB may have dualistic influences depending on the cellular context, strength and persistence of signals, and other microenvironmental factors. This nascent area of inquiry, if proven of broader relevance, may help us reassess our understanding of the inflammation - cancer connection.

4. NF-κB in inflammation-associated cancer

Up-regulated or constitutive expression of NF-κB has been identified in many forms of cancer such as pancreatic cancer (21,49), hepatocellular carcinoma (50,51) and colorectal cancer (52,53). NF-κB itself has been considered a tumor-initiator (54). Furthermore, mutations in *c-Rel*, *p100*, *Bcl-3* and *IκBα*, and constitutive *IKK1* activation are associated with leukemia and lymphoma (55).

Recent findings strongly suggest a relationship between chronic inflammation, NF-κB activation and cancer development. Several groups assessed the contribution of NF-κB activation to carcinogenesis by manipulating individual components of this signaling cascade. For example, to elucidate the role of constitutive NF-κB activation in human pancreatic cancer cells, Fukioda *et al* generated pancreatic tumor cell lines expressing a phosphorylation defective IκBα (IκBαM) that blocks NF-κB activity (56). Using these cell lines, they demonstrated in an orthotopic nude mouse model that inhibition of constitutive NF-κB activity (by expressing IκBαM) suppressed the tumorigenicity of these cells. This finding underscores the critical role of NF-κB in the development of pancreatic adenocarcinoma.

Using a colitis-associated cancer model, Greten *et al* showed that although deletion of IKKß in intestinal epithelial cells does not decrease inflammation, it leads to a dramatic decrease in tumor incidence without affecting tumor size. This

is linked to increased epithelial apoptosis during tumor promotion. Deleting IKKß in myeloid cells, however, results in a significant decrease in tumor size. This deletion diminishes expression of proinflammatory cytokines that may serve as tumor growth factors, without affecting apoptosis. Thus, specific inactivation of the IKK/NF-κB pathway in two different cell types can attenuate formation of inflammation-associated tumors. In addition to suppressing apoptosis in advanced tumors, IKKß may link inflammation to cancer (57).

Another study by Pikarsky *et al* demonstrated a crucial role for NF-κB signaling in inflammation-induced hepatocellular carcinoma (13). Their model system was an *MDR2*-knockout mouse strain that spontaneously develops chronic hepatitis and subsequently hepatocellular carcinoma. These mice carried genes enabling tetracycline-inducible, liver-specific expression of a super-repressor of NF-κB signaling; this signaling suppressor was an IκBα molecule that could not be phosphorylated and therefore retained p65-p50 in the cytoplasm. In these mice, NF-κB activation in liver cells could be selectively inhibited during tumor initiation or promotion. NF-κB inhibition during tumor initiation (first seven months) did not inhibit the development of hepatitis, nor did it affect hepatocyte transformation. By contrast, suppressing NF-κB inhibition in later stages of tumor development (through anti-TNF-α treatment or induction of an IκB-super-repressor) resulted in apoptosis of transformed hepatocytes and failure to progress to hepatocellular carcinoma. They concluded that NF-κB is essential for promoting inflammation-associated cancer, and is therefore a suitable target for cancer prevention in chronic inflammatory diseases.

These and other observations make a strong case for the connection between inflammation and cancer and the role of NF-κB in it. Although there are reservations as to whether NF-κB may be involved in tumor initiation, its activation has a role in tumor promotion at least by preventing apoptosis of premalignant cells. At the same time, NF-κB activation in tumor-associated inflammatory cells contributes to tumor growth by inducing synthesis of tumor-promoting proinflammatory mediators. Thus, blocking one or more components of the NF-κB cascade can arrest or greatly attenuate the carcinogenic process (10,58).

5. The critical role of NF-κB in pancreatic carcinogenesis

The first evidence that NF-κB plays a major role in malignant transformation came from the development of aggressive tumors in chickens, following the transfer of *v-rel*, a highly oncogenic viral homolog of *c-rel*, which is an NF-κB/Rel protein. The role of NF-κB in oncogenesis has been established in the last few years (4-6,11). Many reports demonstrate that members of the NF-κB and IκB families are involved in the development of cancer. NF-κB is up-regulated through chromosomal changes or constitutive activation in various hematological malignancies such as lymphomas, and in solid tumors, including pancreatic, breast, ovarian, colon and prostate cancer (6).

Three lines of evidence indicate that NF-κB plays an essential role in pancreatic cancer. First, NF-κB is constitutively activated in 70% of human pancreatic cancers and in human pancreatic cell lines such as BxPC-3 (49), PANC-1 (21) and MIA PaCa-2 (59), but not in normal pancreatic tissues or in immortalized, non-tumorigenic pancreatic epithelial cells. Furthermore, activation of NF-κB has been observed in animal models of pancreatic cancer (61) and in human pancreatic tissue (59). Second, supporting evidence for the role of NF-κB in pancreatic carcinogenesis has been obtained from the study of various pancreatic cell lines and tumor models. For example, suppression of NF-κB DNA activation restored apoptosis in pancreatic cancer cells (61), whereas treatment with various NF-κB inhibitors or transfection of the IκBα super-repressor strongly enhanced the apoptotic effect of etoposide (VP16) or doxorubicin in resistant pancreatic cancer cells (62). Inhibition of constitutive NF-κB activity by IκBαM suppressed pancreatic carcinogenesis (56,63). Increased expression of NF-κB subunits has been found in human pancreatic cancer cells (49). And, third, NF-κB may participate in early events in pancreatic carcinogenesis. This is evidenced by the interactions of NF-κB with pathways involving known early players [e.g., the *ras* oncogene (59)] or apoptosis resistance that precedes formation of invasive pancreatic cancer (reviewed in ref. 4). It has been suggested that by promoting proliferation and inhibiting apoptosis, NF-κB tips the balance between proliferation and apoptosis toward malignant growth in tumor cells (64). Our own findings of NF-κB activation and suppression of apoptosis during neoplastic changes in the hamster pancreas are consistent with this notion (65).

Pancreatic carcinoma has been associated with both chronic and hereditary pancreatitis. Chronic pancreatitis increases the risk of developing pancreatic cancer 15- to 16-fold compared to that of the general population (12,66). Pancreatitis illustrates the contribution of both inflammation and NF-κB to carcinogenesis.

In experimental models of pancreatitis, activation of NF-κB is an early response to inflammation, leading to the secretion of proinflammatory cytokines, such as transforming growth factor alpha (TGFα) and IL-1ß (16,67,68). Concomitant activation of endothelial cells and recruitment of activated macrophages to the site of damage enhance cytokine release and induce expression of acute phase genes such as COX-2 and IL-8 (69,70). Expression of acute phase genes together with the enhanced expression of adhesion molecules such as vascular cell adhesion molecule, intercellular adhesion molecule, E- and P-selectins on endothelial cells serve as a signal for the recruitment of the leukocytes to the site of the damage (71). Leukocytes are the main source of reactive oxygen species and nitric oxide, which have a significant deleterious effect on DNA and act as a strong inducer of apoptosis. Oxidative stress can also activate transcription factors such as NF-κB and activator protein-1 (AP-1), which will activate survival and growth promoting signaling pathways and further cytokine release (15). Increased mitogenic signals in an environment rich in oxidative species may create a selective pressure to acquire mutations favoring survival and uncontrolled proliferation which may give rise to cancer.

Fibrosis is a hallmark of human pancreatic adenocarcinoma and chronic pancreatitis. Under normal conditions, pancreatic stellate cells remain quiescent. However, during inflammation, these cells are stimulated by cytokines and growth factors, such as TGF-ß1, TGF-α and platelet-derived growth factor to proliferate and differentiate into myofibroblasts (73). Myofibro-

blasts then express smooth muscle actin and secrete extracellular matrix (ECM) proteins such as collagen types I and III, and fibronectin which replace the necrotic tissue (73). In addition, fibrosis contributes to tissue damage by secreting matrix metalloproteinases to destroy the normal ECM and deposit newly formed fibrotic ECM components (75-77). Activated fibroblasts also produce growth factors which are involved in proliferation of the injured tissue, facilitating neoplastic conversion (73). Thus, the dysregulation of fibrogenesis in pancreas appears to be an important factor in inflammation-associated pancreatic carcinogenesis.

6. NF-κB as a chemoprevention target

Converging data indicate that NF-κB is an ideal target for chemoprevention (77). Most chemopreventive agents modulate NF-κB activity. They suppress the activation of NF-κB through inhibition of the NF-κB signaling pathway and sensitize tumors to chemotherapeutic agents through abrogation of NF-κB activation. In addition, several studies have shown that conventional NSAIDs, the prototypical chemopreventive agents, modulate the NF-κB pathway. For example, Kopp and Ghosh were the first to demonstrate that aspirin (ASA) inhibits the activation of NF-κB without interfering with the transcriptional machinery of the cell (78). Prolonged treatment of colorectal cancer cells with aspirin decreases cytoplasmic IκBα and thus increases translocation of NF-κB to the nucleus; such activation of the NF-κB pathway induces apoptosis in these cells (79). Sulindac also inhibits activation of the NF-κB pathway (48,80).

Recently, Sclabas *et al* using an orthotopic mouse model with human pancreatic carcinoma cell lines showed that aspirin prevents pancreatic carcinoma (21). Aspirin inhibited constitutive NF-κB activation in cultured cells and, in turn, decreased the expression of the downstream target gene COX-2 without significantly inhibiting their *in vitro* growth. The authors speculated that inhibition of NF-κB activation is a possible mechanism for aspirin's preventive effect in pancreatic carcinoma and that such an effect represents a mechanistic link between inflammation and tumorigenesis. Given the controversy as to whether aspirin indeed prevents pancreatic cancer in humans and the conjectural nature of the effect of aspirin on NF-κB activation in their *in vivo* model, there is some doubt regarding the ultimate relevance of these findings to humans.

Like all cancers, pancreatic cancer reflects changes in the rates of proliferation (increase) or of apoptosis (decrease) or of both. Persistent NF-κB activity alters the expression of genes that control cell proliferation/cell cycle and also apoptosis (81). The following sets of data highlight this notion and provide the rationale for considering NF-κB as an important signaling molecule in pancreatic cancer and hence a suitable chemoprevention target.

NF-κB regulates cell proliferation/cell cycle in the pancreas. The role of NF-κB in this regard has been documented in pancreatic cancer lines (59,82) and in xenotransplanted human pancreatic cancer cells (83). NF-κB-dependent proliferation and cell cycle genes include $p21^{WAF1}$, cyclins (D1, D2, D3), *myc* and *rel* (81). It is important to note that $p21^{WAF1}$ can, under certain circumstances, affect both proliferation/cell cycle and apoptosis (84). Regarding the D cyclins, it is worth mentioning that *cyclin D1*, which regulates the G_1-to-S transition, has upstream regulatory κB binding sites. In general, cyclin D1 is a key player in the control of cell proliferation in cancer. For example, in certain breast cancers, cyclin D1 expression is increased directly by persistent NF-κB activation (81). Thus it is plausible that the same takes place in pancreatic cancer as well, although this point requires documentation.

Table II. NF-κB inhibitors for prevention of pancreatic cancer.

NF-κB inhibitor	Function	Refs.
Aspirin and aspirin-like drugs (e.g., NO-aspirin)	Suppression of proliferation; induction of apoptosis	(67) (21)
Genistein	Inhibition of cell growth; induction of apoptosis	(22)
Curcumin (Diferuloylmethane)	Suppression of proliferation; induction of apoptosis	(23)
Parthenolide and sulindac	Inhibition of cell growth	(91)
Etoposide (VP16) and doxorubicin	Induction of apoptosis	(62)

NF-κB has anti-apoptotic activity in cancer in general (reviewed in ref. 85), and in pancreatic cancer in particular (reviewed in refs. 4,20). Important apoptosis genes that are NF-κB targets and may be related to malignancy include Bcl-X_L, Bcl-2, IAPs and TRAF (81). NF-κB is a direct activator of Bcl-X_L expression (86) and Bcl-X_L plays a key role in NF-κB mediated anti-apoptotic signaling cascades in pancreatic cancer (4,87). A compelling case for Bcl-XL was made recently by a study in transgenic mice overexpressing TGFα, which develop pancreatic cancer. Up-regulation of Bcl-X_L is early and persistent. NF-κB increases Bcl-X_L expression in the pre-malignant lesions and tumor cells. Blocking NF-κB induces apoptosis in pancreatic tumor cells (88). Table II lists agents used in the prevention of pancreatic cancer thought to act by inhibiting NF-κB.

Consistent with this notion is our recent study of the chemopreventive effect of nitric oxide donating aspirin (NO-ASA), an ASA bearing a NO-releasing moiety (65). Using the female Syrian golden hamster model of pancreatic cancer, we observed that pancreatic carcinogenesis was associated with NF-κB activation: from undetectable in normal tissue, it increased progressively, reaching its maximum in cancer (17-fold over the level noted in PanIN1A). In parallel, apoptosis was suppressed and proliferation enhanced. NO-ASA dramatically reduced the incidence and multiplicity of pancreatic cancer (89 and 94%, respectively). Compared to controls, NO-ASA inhibited NF-κB activation during all stages of carcinogenesis, being most pronounced during the PanIN1B and PanIN2 stages. The proliferation/apoptosis ratio was also progressively decreased. In contrast, conventional aspirin had no chemopreventive effect and also failed to affect the activation of NF-κB during carcinogenesis.

7. Conclusions and future perspectives

The last decade has witnessed a subtle but important shift in our thinking on cancer pathogenesis. It is now clear that inflammation is an important proximal player in the cascade of events that culminate in the abnormal and aggressive malignant phenotype that all too often succeeds in killing its host organism.

It is worth noting that it took over 100 years between Virchow's observations and the current interest in inflammation as it relates to cancer. This long delay reflects the requirement for a more sophisticated understanding not only of inflammation but also of cancer. In fact, the conceptual leap to the potential relevance of inflammation to cancer has followed the shift from microscopic observations (leukocytic infiltrates) to the molecular aberrations that underlie inflammation and cancer. Up until recently, inflammation, scant as it often is in microscopic terms, had failed to generate enough enthusiasm as a plausible pathogenetic mechanism. Current appreciation of the biology of NF-κB is helping change this in a major way. NF-κB is a pivotal molecule not only in inflammation but also in inflammation-associated cancer. Its controlling position over a diverse (and large) group of genes allows it to modulate an extensive array of biological responses. There now exists strong evidence, if not conclusive proof, that NF-κB links inflammation and cancer and that specific inactivation of NF-κB is a promising tool to attenuate the formation of inflammation-associated tumors. Thus, it is likely that continuing study of NF-κB's role in carcinogenesis, already attracting major interest, will provide opportunities for cancer prevention and perhaps treatment.

In many respects, NF-κB represents a highly-promising but little-exploited target for the chemoprevention of cancer, including that of the pancreas. The development of agents directed at components of the NF-κB pathway represents a pressing need; ongoing efforts in this area, if successful, will have a major impact on this field.

It is a rather safe prediction that the next few years will almost certainly enhance our understanding of NF-κB biology; solidify its role as a major link between inflammation and cancer; and utilize such knowledge to develop NF-κB-centered strategies to prevent cancer. Pancreatic cancer prevention is an area where progress based on such manipulations of the NF-κB signaling cascade should be forthcoming.

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