

Potential prognostic and therapeutic roles for cytokines in breast cancer (Review)

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Abstract. Cytokines are known to have both stimulatory and inhibitory effects on breast cancer growth depending on their relative concentrations and the presence of other modulating factors in the tumour microenvironment. Certain cytokines appear to prevent an effective immune response being mounted, permitting cancer growth, whereas others promote the immune system's anti-tumour capability. Furthermore, the systemic levels of certain cytokines, e.g. IL-6 and IL-18, independently show promising correlations with disease stage and progression. With advances in methods for delivery of cytokines to a tumour site, the enhanced induction of anti-tumour immunity by targeted cytokine release is becoming a realistic option. Here, we review the role of cytokines in the immune response against breast cancer and assess their potential as prognostic indicators and/or use in immune therapy. A literature search was conducted using Medline, restricted to articles published in the English language, using combinations of the following MeSH terms: cytokines, breast cancer, immunology, immunotherapy and interleukins. Focused searches using keywords relevant to the role of cytokines in breast cancer immunology yielded >200 references.

Contents

1. Introduction
2. Cytokines with potential as prognostic markers
3. Cytokines with potential therapeutic roles

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Abbreviations: NK, natural killer; IL, interleukin; IFN, interferon; TNF- α , tumour necrosis factor- α ; TGF- β , transforming growth factor- β ; LAK, lymphokine activated killer; PGE₂, prostaglandin E₂; DC, dendritic cells; TIL, tumour infiltrating lymphocytes; CTL, cytotoxic T lymphocytes; GM-CSF, granulocyte macrophage colony stimulating factor; LPS, lipopolysaccharide; PMN, polymorphonuclear cells; Mig, monokine induced by IFN- γ ; IP-10, inducible protein 10

Key words: cytokines, interleukin, breast cancer

4. Cytokines with potential prognostic and therapeutic roles
5. Summary

1. Introduction

Breast cancer is a complex disease; its aetiology is multifactorial, the period of development can span decades and clinical course is highly variable. Breast cancer is the most common malignancy in women, accounting for approximately one third of all female cancers. Around 41,000 women are diagnosed with breast cancer each year in the UK and there were 12,800 deaths due to the disease in 2002 (1). Both the innate and acquired arms of the immune system are believed to play crucial roles in the anti-tumour response, and the interaction between host immune system and tumour cells has been the subject of intense research over the past decades (2,3). Cytokines including transforming growth factor- β (TGF- β), tumour necrosis factor- α (TNF- α), interleukins IL-1, IL-6, IL-10, IL-12, IL-18 and the interferons all play a key role in controlling the immune response. Changes in cytokine levels mediated by the tumour both directly and indirectly are important parameters that affect the course of disease.

Briefly, cytokines are secreted principally by lymphocytes and macrophages and act by altering the function of target cells in a paracrine, autocrine or endocrine (less commonly) fashion. Cytokines have several common structural and functional characteristics: a) they tend to be glycosylated polypeptides; b) they are biologically active at very low concentrations; c) they exert their effects by binding to receptors on the target cell surface; d) they are pleiotropic; and e) their effects are additive, synergistic or antagonistic. Therefore, it is the integration of these effects that determines the overall outcome. Furthermore, it should be remembered that the cytokine network possesses a high level of redundancy, i.e. multiple cytokines mediating the same effect.

It has been known for a number of years that there is a significant impairment of the immune system in breast cancer patients (4). The lack of an effective immune response to tumourigenesis, in spite of the presence of tumour infiltrating lymphocytes (TIL) *in vivo*, is believed to be due in some way to the action of 'inhibitory' cytokines in the tumour microenvironment. Also, breast cancer has long been considered to be weakly immunogenic and, hence, is only poorly recognised by the immune system, meaning that this type of tumour is generally thought to be a poor candidate for immune therapy

(5). In contrast to many of the *in vivo* observations, however, certain cytokines have been demonstrated to promote the generation and/or efficacy of anti-tumour effectors, including dendritic cells (DC) and lymphokine activated killer (LAK) cells and cause inhibition of tumour growth or, in certain instances, regression. Most of this work has been *in vitro* although some *in vivo* data do exist. In addition to their effects on the immune system, cytokines have also been reported to influence aromatase activity and oestrogen synthesis directly in the tumour vicinity and hence promote tumour growth and aggressiveness (6).

Here, we review the role of cytokines in the host immune response against breast cancer and evaluate their potential as prognostic markers for assessing disease stage, tumour aggressiveness and disease progression. In addition, the possible role of individual cytokines in novel immune therapy regimens is critically considered.

2. Cytokines with potential as prognostic markers

Transforming growth factor- β (TGF- β) is a pleiotropic cytokine produced by numerous tumour types. It is known to induce angiogenesis, impair DC functions *in vitro*, block T-cell activation, mediate the production of the extracellular matrix (ECM) and facilitate the production of cytokines by fibroblasts and endothelial cells. Its role in breast cancer carcinogenesis has been comprehensively reviewed by Benson (7).

There are two major studies of interest with respect to TGF- β 1 and breast cancer prognosis. Firstly, Ivanovic *et al* (8) investigated the association between plasma TGF- β 1 level and disease progression in advanced breast cancer patients (n=44). They found that plasma TGF- β 1 values were significantly elevated ($P<0.05$) in stage IIIB/IV patients compared with healthy donors, suggesting that TGF- β 1 may have potential as a prognostic marker for breast cancer patients with advanced disease and is worthy of further investigation. Secondly, Kobie *et al* (9), observing the lack of effectiveness of DC-based vaccines in treating established tumours, demonstrated that TGF- β exposure inhibits the ability of DC to present antigen and stimulate a specific T-cell response. Furthermore, blocking of TGF- β with the neutralizing monoclonal antibody, 2G7, enhanced the ability of DC vaccines to inhibit the growth of established 4T1 murine mammary tumours. Treatment of 4T1 tumours transfected with TGF- β with a combination of DC and 2G7 monoclonal antibody inhibited tumour growth and resulted in the complete regression of tumours in 40% of mouse *in vivo* models. These results clearly suggest that neutralization of TGF- β is an important factor to be considered when designing DC vaccines for clinical use in humans as it is seen to enhance the efficacy of DC-based vaccines in murine models.

Interleukin-6 (IL-6) is a pluripotent cytokine produced by monocytes, macrophages, lymphocytes, endothelial cells and intestinal epithelial cells and its expression is known to be induced by IL-1, TNF- α and platelet activating factor. IL-6 promotes B-cell maturation and differentiation, stimulates T-cell proliferation and differentiation, stimulates the hypothalamo-pituitary-adrenal axis and induces production of acute phase reactants (10).

Benoy *et al* (11) found that the serum IL-6 concentration is significantly higher in patients with breast cancer compared with healthy controls (n=26; $P<0.0001$). Median IL-6 serum levels were nearly 10 times higher in patients with metastatic breast cancer (n=73) as compared to those with locoregional disease (n=31) (6.0 pg/ml versus 0.7 pg/ml respectively). Similarly, Yokoe and colleagues (12), in a small preliminary study, reported that continuously elevated serum IL-6 levels correlate to poor survival in patients with hormone-refractory metastatic breast cancer (n=12). They also reported that pre-treatment IL-6 and IL-8 levels are predictive indicators of response to therapy and prognosis of patients with recurrent breast cancer. This was confirmed more recently by Bachelot and colleagues (13), in a study involving 87 patients with hormone-refractory metastatic breast cancer. Thirty-nine percent of patients had detectable serum levels of IL-6 and high levels were significantly correlated to a shorter survival. In a multivariate analysis together with clinical prognostic parameters, serum IL-6 was identified as an independent adverse prognostic variable for overall survival ($P<0.001$). Similar associations between IL-6 levels and disease progression and survival have also been reported in patients with non-small cell lung cancer and prostate cancer.

Interleukin-8 (IL-8) is secreted by monocytes, macrophages and endothelial cells. Also classified as a chemokine, it stimulates chemotaxis and triggering of degranulation of neutrophils, increased expression of surface adhesion molecules and production of reactive oxygen metabolites (14).

Lin and colleagues (15) reported that elevated expression of IL-8 in human breast cancer cell lines was associated with breast cancer invasiveness and angiogenesis. Furthermore, IL-8 levels are inversely related to oestrogen receptor (ER) status with ER-positive cells generally expressing low levels and ER-negative cells expressing higher levels of IL-8. Bendre *et al* (16) demonstrated a direct effect of IL-8 on osteoclast differentiation and activity, implying a possible role in osteolysis, an event frequently associated with metastatic breast cancer. IL-8 levels were found to be significantly increased in breast carcinoma patients and were correlated with stage of disease. It has been suggested previously (12) that IL-8 measurement may be useful in estimation of disease progression in women with breast carcinoma, and we consider this to be one of the most promising predictive factors for clinical prognosis.

3. Cytokines with potential therapeutic roles

Tumour necrosis factor- α (TNF- α) is principally produced by lymphocytes and NK cells. TNF- α exhibits various anti-tumoural effects, including the induction of apoptosis and necrosis, activation of cytolytic effector cells and upregulation of expression of intercellular adhesion molecule-1 (ICAM-1) on tumour cells, an important event in the interaction with LAK cells (17).

Jablonska (18) demonstrated that spontaneous production of TNF- α by polymorphonuclear cells (PMN) in breast cancer patients was lower than that found in healthy controls. This lower level of TNF- α production by cancer patients was also seen following *in vitro* stimulation with Zymosan or LPS. However, there were no significant differences in circulating



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els of TNF- α between breast cancer patients and healthy carriers of BRCA1 mutations. More recently, Zielinski *et al* (19) reported impaired production of TNF- α by monocytes derived from patients with breast cancer as well as in healthy carriers of BRCA1 mutations. Whether these changes are caused by the tumour or are the result of the anti-tumour response needs to be elucidated as this knowledge could facilitate new therapeutic approaches.

Tsuge and colleagues (20) found that infiltration of breast cancer lesions by DC, an important subset of antigen-presenting cells characterised by their potent capacity to activate naïve T cells, requires expression of TNF- α , along with granulocyte macrophage colony stimulating factor (GM-CSF) and IL-1, on cancer cells. Candido *et al* (21) investigated whether intra-tumoural delivery of DC alone would have any anti-tumour effect on a malignancy with a relatively high apoptotic index. Their studies revealed intense mononuclear cell infiltration during and after DC injections and significant apoptosis of the tumour cells. They also reported that the level of tumour apoptosis could be increased substantially by co-administration of TNF- α with DC. Manna and Mohanakumar (22) reported that human peripheral blood DC activated by pro-inflammatory stimuli produce TNF- α which, subsequently, has a potent direct anti-tumour effect against breast cancer cell lines *in vitro*, leading to growth inhibition and apoptosis. Based on the above observations, it is plausible that TNF- α could be included as part of an immunotherapeutic regime. However, the potential side effects of any such strategies, including possible induction of an autoimmune response due to generalised T cell activation, would need to be carefully considered.

Interferon- γ (IFN- γ) is a pro-inflammatory mediator produced principally by T cells (CD4+ve and CD8+ve) and NK cells. Key functions include activating cells of the monocyte/macrophage lineage, promoting differentiation of naïve CD4+ve T cells into Th1-like cells and inhibiting differentiation of CD4+ve cells into Th2-like cells (23).

Pulaski *et al* (24) demonstrated that IFN- γ is a critical component in regulating an innate phagocytic response against metastatic breast cancer. Furthermore, Kamamura and colleagues (25) incubated peripheral blood mononuclear cells (PBMC) from breast cancer patients with IFN- γ and found that this increased the LAK activity. The use of intravesical instillation of recombinant IFN- γ has been demonstrated to be effective against tumour recurrence in patients with early-stage superficial transitional cell bladder cancer (26). For this to be feasible in breast cancer, new delivery systems allowing targeted cytokine release are required.

Interleukin-10 (IL-10), originally called cytokine synthesis inhibitory factor, is produced primarily by Th2-like cells and activated monocytes. IL-10 is a pleiotropic cytokine that can be immunosuppressive or immunostimulatory depending on its relative concentration in the local microenvironment. IL-10 is a potent modulator of monocyte/macrophage function at many levels, principally through inhibition of antigen-stimulated cytokine synthesis by PBMC. It also downregulates MHC class II expression on macrophages and inhibits their accessory and antigen-presenting functions. Furthermore, IL-10 promotes naïve CD4+ve T cells towards a Th2-like phenotype, downregulating the secretion of IFN- γ and IL-2 by activated Th1-like cells and inhibiting T cell activation and proliferation (27).

Venetsanakos and colleagues (28), when investigating the expression of cytokine mRNA in human breast tumour sections by reverse transcriptase-polymerase chain reaction (RT-PCR), detected significant levels of IL-10 mRNA in tumour tissue with little/no expression in normal breast tissue. Hence, it was postulated that the reduced function of TIL is related to IL-10 concentration, which has known inhibitory effects on T-cell activation. However, IL-10 has also been demonstrated to have potent anti-tumour activity. Dorsey *et al* (29) demonstrated that systemic administration of recombinant human IL-10 to animals bearing established, highly malignant, mammary tumours led to significant growth inhibition which was associated with increased numbers of CD4+ve cells and production of Mig (monokine induced by IFN- γ) and IP-10 (inducible protein 10). Mig and IP-10 are chemotactic for activated T and NK cells and potent inhibitors of angiogenesis. Furthermore, Kundu and Fulton (30) have reported an anti-metastatic activity of IL-10 which is believed to be dependent on NK activity. They showed that IL-10 expression down-regulates MHC class I expression on tumour cells, leading to enhanced NK lysis. This dual role for IL-10 is now thought to be due to its concentration in the tumour microenvironment with low concentrations (picograms) facilitating tumour growth but higher concentrations (nanograms) having considerable anti-tumour activity. The potency of IL-10 has been clearly demonstrated; however, once again it may prove a difficult reagent to use therapeutically because of the obvious potential for unwanted, deleterious, immunosuppression.

Interleukin-12 (IL-12), also known as natural killer cell stimulatory factor or cytotoxic lymphocyte maturation factor, is another pleiotropic cytokine principally produced by monocytes and macrophages. IL-12 is a pivotal factor for the initiation of cellular immunity and has been shown to have multiple effects on T cells and NK cells. IL-12 promotes the polarization of Th1-like T-cell development, increases the differentiation and activation of cytolytic T cells and, in concert with TNF- α , IL-1, IL-2 and IL-18, induces IFN- γ production by T cells and NK cells. The activities of IL-12 are antagonized primarily by IL-10 which, as described above, is associated with the development of naïve T helper cells into Th2-like cells and mediation of the humoral immune response. IL-10 inhibits IFN- γ production by suppressing the transcription of the IL-12 gene (31). Like IL-1, IL-12 is not essential for the generation of CTL, however, its addition (either exogenously or endogenously) or inhibition markedly improves or inhibits CTL development respectively (32).

Cavallo *et al* (33) demonstrated the anti-tumour effects of local and systemic recombinant murine interleukin-12 (rIL-12) in mice harbouring spontaneously metastasising mammary adenocarcinomas. Leukocyte infiltration of the tumour site and production of mRNA for secondary cytokines (mainly IFN- γ) and chemokines all occurred more quickly and were more effective in mice receiving systemic rather than local rIL-12. Sabel and colleagues (34) more recently demonstrated that intra-tumoural administration of poly(lactic-acid)-encapsulated microspheres (PLAM) containing IL-12, TNF- α and GM-CSF, in a second murine model of breast cancer, enhanced CD8+ve T-cell infiltration resulting in tumour regression. Importantly, it also induced tumour-specific T cells in the lymph nodes and spleen, resulting in a memory immune response.

A number of therapeutic vaccination strategies have been developed over the past few years, many of which include DC. These professional antigen-presenting cells express an array of co-stimulatory molecules as well as secreting potent pro-inflammatory cytokines with IL-12 playing a significant role. Luft *et al* (35) demonstrated that human DC co-activated *in vitro* by CD40L and IL-1 β produce high levels of IL-12 and, subsequently, IFN- γ and thus become potent T-cell stimulators. The dual CD40L/IL-1 signal enables the production of pro-inflammatory cytokines, including IL-1, IL-12, IL-18 and IFN- γ by DC, and enhances the differentiation of naïve T cells into effectors of a Th1 cellular immune response. Hence, it is predicted that such DC will function as effective vaccines for the induction of cellular immunity *in vivo*. Once again, the challenge now is to translate the findings from murine models to human subjects (35). Pedersen *et al* (36) have shown that DC generated *in vitro* from breast cancer patients have similar antigen-specific reactivity against infectious agents to DC from normal donors but have a significantly decreased allostimulatory ability, suggesting that further manipulation of these cells is required prior to use *in vivo*. A recent review has noted, however, that caution is needed in interpreting data on DC vaccination strategies and has highlighted the need for clinical response to be the main means of assessment of efficacy (37).

Interleukin-24 (IL-24) exhibits homology to IL-10 and is found within the IL-10 family gene cluster. It is secreted by activated monocytes and T cells and is generally considered to have tumour suppressive activity. IL-24 was initially described as melanoma differentiation-associated gene 7 (mda-7) (38).

Overexpression of IL-24 is growth inhibitory for a range of human tumour cells. Su *et al* (39), using a nude mouse model, showed that breast tumour cells transfected with IL-24 underwent apoptosis, whereas the same cell line established tumour masses when IL-24 was given exogenously. It appears that IL-24 mediates its anti-tumour effects in a p53-independent manner. The endogenous mode of action of IL-24 has been shown *in vivo* through infection via adenoviral vectors. McKenzie and colleagues (40) evaluated the impact of combination therapy of a recombinant adenovirus vector encoding human IL-24 and Herceptin on Her-2/neu-overexpressing breast cancer cell line MCF-7-Her-18 *in vitro* and in a nude mouse model *in vivo*. The combination therapy resulted in growth inhibition *in vitro* and a marked reduction in tumour size *in vivo*. IL-24 has generated considerable interest as a novel tool for cancer gene therapy and is currently undergoing phase II clinical trials to determine its efficacy in patients.

4. Cytokines with potential prognostic and therapeutic roles

Interleukin-2 (IL-2) was originally identified as a growth factor for T lymphocytes. It is produced mainly by CD4⁺ve Th1-like cells and its key features include promotion of T-cell and activated B-cell proliferation, increased secretion of pro-inflammatory cytokines by T cells and increased cytotoxicity of NK cells (41).

Reduced IL-2 production has been described as one of the most frequent immune dysfunctions observed at relapse in patients with disseminated solid neoplasms. Arduino *et al*

(42) reported that patients with breast cancer had a much lower rate of relapse (4.7%) if plasma IL-2 levels were normal compared with those patients with decreased amounts (33.3%) one year post-operatively. Not only have systemic levels been shown to vary in cancer patients but also IL-2 production by lymphocytes in the tumour vicinity is reported to be impaired and it is suggested that this decrease will limit the cytotoxic potency of CTL (43).

It is well-known that hypoxia is a common event within a tumour mass and it has been postulated that this can affect the ability of tumour cells to be recognized by the immune system. Lee *et al* (44) showed that IL-2-transfected tumours showed decreased hypoxia and increased vascularization compared with parental tumours and these changes were associated with a pronounced infiltration of activated T cells. Thus, expression of IL-2 at the tumour site may enhance immunity not only by inducing the generation of reactive CTL but also by allowing increased infiltration of these activated cells into the tumour mass.

A number of positive clinical results have been observed after IL-2 treatment in a variety of solid tumours, e.g. melanoma, pulmonary metastasis of renal carcinoma, unresectable pancreatic head carcinoma and malignant mesothelioma. In contrast, IL-2 therapy for breast cancer has not been generally effective although, recently, peri-tumoural administration of IL-2 was reported to significantly improve survival in mice with advanced and relatively aggressive tumours (45). Furthermore, in a phase-I trial with HER2-overexpressing metastatic breast cancer, Repka and colleagues (46) reported encouraging results when Trastuzumab was used in combination with IL-2. In this pilot study, ten women with metastatic breast cancer received multiple cycles of IL-2 and Trastuzumab and no significant toxicities were seen. Clinical responses were: one partial response, five cases of stable disease, and four cases of progressive disease. Immune assays *in vitro* showed NK cell expansion and Trastuzumab-mediated increased NK killing of breast cancer targets, although this immune parameter did not correlate positively with clinical response. This study suggests that IL-2 can be safely administered without inducing significant toxic side effects and that further work is required to ascertain the mechanism of action.

Interleukin-18 (IL-18), a more recently described member of the IL-1 cytokine superfamily, is now recognised as an important regulator of innate and acquired immune responses. Formerly called interferon- γ -inducing factor (IGIF), IL-18 is a cytokine that plays an important role in the Th1 response, primarily by its ability to induce IFN- γ production by T and NK cells. IL-18 is produced early during the acute immune response by macrophages and immature DC. In addition to IFN- γ , IL-18 also induces GM-CSF, TNF- α and IL-1 expression and acts in collaboration with IL-12 (47).

Coughlin *et al* (48) studied the anti-tumour mechanisms activated by murine IL-12 and IL-18, cytokines that induce IFN- γ production, using a transfected murine mammary carcinoma model. Cells expressing mIL-12 or mIL-18 were less tumorigenic and formed tumours more slowly than non-transfected control cells. Antibody neutralization studies revealed that the anti-tumour effects of secreted mIL-12 and mIL-18 were mediated via IFN- γ .



Summary of cytokines with a potential role as prognostic markers in breast cancer.

Cytokine	Reported changes in breast cancer patients	Refs.
TGF- β	Raised levels in patients with advanced disease (n=44; P<0.05).	(8)
IL-2	Decreased levels associated with relapse.	(42)
IL-6	Raised levels in patients with metastases (n=73; P<0.0001). Levels correlate to survival and response to therapy (n=87; P<0.001).	(11-13)
IL-8	Levels increased in advanced disease and increase with disease progression.	(55)
IL-18	Raised levels in breast cancer patients (n=56; P<0.05). Levels higher in patients with metastases (n=38; P<0.001).	(52,53)

Table II. Summary of cytokines with a potential role in immune therapy of breast cancer.

Cytokine	Proposed mode of action	Refs.
TNF- α	Enhances anti-tumour effect of DC-based vaccines. Inhibits growth and promotes apoptosis of tumour cells in breast cancer cell lines <i>in vitro</i> .	(21,22)
IFN- γ	Enhances LAK activity.	(25)
IL-1	Important role in activation of DC and generation of CTL. Effective as adjuvants in DC-based vaccines.	(35,36)
IL-2	Enhances tumour infiltration by CTL. When used with Trastuzumab in phase-I trials, enhances ADCC and NK cell lysis of breast cancer cells.	(44,46)
IL-10	Inhibits tumour growth in murine models of breast cancer by elaboration of chemokines, inhibition of angiogenesis and stimulation of NO production. Has potent anti-metastatic activity by inducing NK lysis of tumour cells.	(29,30,56)
IL-12	Demonstrated to induce tumour destruction in murine models of breast cancer by inhibiting angiogenesis and activating CTL.	(33,34)
IL-18	Facilitates tumour rejection by augmenting cytotoxic effects of NK cells and T cells and inhibiting angiogenesis. Enhances anti-tumour effect of DC-based vaccines. Suppresses development of bone metastases in murine models.	(48-51)
IL-24	Induces selective apoptosis of tumour cells in murine models of breast cancer while sparing normal mammary epithelial cells.	(39,40)

IL-18 also appears to be a potent stimulator of DC function, enhancing *in vitro* tumour vaccination strategies by increasing recruitment of Th1 cytokine-producing cells and, thus, increasing numbers of antigen-specific CD8+ve T cells when transfected into DC (49). Nakata *et al* (50) investigated the effects of IL-18 on bone metastasis of human breast cancer MDA-231 cells in a nude mouse model. IL-18 was found to inhibit osteolytic growth at bone metastatic sites and suppressed an early onset of bone metastasis. Furthermore, systemic daily administration of mIL-18 significantly inhibited the number and total area of osteolytic bone metastases by the RWGT2 human lung cancer cells in nude mice. Thus, IL-18 may be useful clinically for suppression of osteolytic bone

metastasis in patients with advanced breast cancers. However, the problem of the unwanted systemic effects of IL-18 still remains to be overcome (50,51).

Two relevant human studies using IL-18 have been conducted; the first, by Gunel *et al* (52), reported that serum IL-18 levels were significantly increased in breast cancer patients (n=56; P<0.05) when compared with controls (n=14). This change was found to be associated with established clinically-used prognostic factors, such as tumour size, axillary lymph node involvement and disease stage. A second study from this group also showed that IL-18 levels were significantly higher in patients with metastatic spread compared with those without (38 metastatic vs. 26-non metastatic patients;

$P < 0.001$). Despite the relatively small cohort size, the findings of these studies suggest that serum IL-18 levels may be useful as a prognostic marker in monitoring breast cancer patients after treatment and/or in tumour surveillance to detect bony metastasis (53). The results from the human studies appear to contradict the data from the murine models and, therefore, further work is required to establish the explanation for this. However, we would suggest that IL-18 is a potent cytokine worthy of further study.

5. Summary

Over the last few decades, a wealth of evidence has been gathered on the role that the immune system plays in the fight against cancer and it is now well established that cytokines are critical in achieving an effective anti-tumour immune response. Breast cancer development and progression is influenced by intrinsic properties of the tumour cells, as well as by macro- and micro-environmental factors. Cytokine kinetics, therefore, represent important immunological phenomena worthy of investigation. Some cytokines will stimulate cancer cell growth and may contribute to loco-regional and/or metastatic spread. The elevation of the serum concentration of such cytokines, however, might be utilized as a marker of immune status, disease prognosis and monitoring (Table I). Alternatively, other cytokines may act as adjuvants in immune therapeutic regimens, boosting any number of specific cell functions (Table II). A key factor that must be considered whenever cytokines are to be administered systemically is the potential induction of side-effects such as serum sickness, myelosuppression and metabolic disturbances. With the miniaturization of drug delivery systems and advances in nanotechnology, however, it is becoming possible to deliver therapeutic agents specifically to target sites, thereby avoiding adverse systemic side effects (54). Having thoroughly reviewed the literature, we believe that cytokines will continue to play a prominent part in future immunotherapeutic interventions using antibodies, DC and cancer vaccines.

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