Cytokines, inflammation and breast cancer

Sandeep Kumar

Aastha Hospice, Lucknow, India. Former Director, All India Institute of Medical Sciences, Bhopal, India

*Corresponding author e-mail: k_sandeep@hotmail.com

ABSTRACT

Infection, cancer, or inflammation triggers the production of immunological mediators termed cytokines. Some cytokines clearly promote inflammation and are called pro-inflammatory cytokines, whereas other cytokines suppress the activity of pro-inflammatory cytokines and are called anti-inflammatory cytokines. For example, IL-4, IL-10, and IL-13 are potent activators of B lymphocytes. However, IL-4, IL-10, and IL-13 are also potent anti-inflammatory agents. They are anti-inflammatory cytokines by virtue of their ability to suppress genes for pro-inflammatory cytokines such as IL-1, TNF, and the chemokines. IL-1 and TNF are inducers of endothelial adhesion molecules, which are essential for the adhesion of leukocytes to the endothelial surface prior to emigration into the tissues. Taken together, pro-inflammatory cytokine mediated inflammation is a cascade of gene products usually not produced in healthy persons. Anti-inflammatory cytokines block this process or at least suppress the intensity of the cascade. Cytokines such as IL-4, IL-10, IL-13, and transforming growth factor (TGF-β) suppress the production of IL-1, TNF, chemokines such as IL-8, and vascular adhesion molecules. Therefore, a "balance" between the effects of pro-inflammatory and anti-inflammatory cytokines is thought to determine the outcome of disease, whether in the short term or long term. This article reviews the functions of the cytokines in relation to breast cancer.

KEYWORDS: Cytokines, Inflammation, Breast Cancer

INTRODUCTION

The presence of leukocytes within tumors, observed in the 19th century by Rudolf Virchow, provided the first indication of a possible link between inflammation and cancer. Yet, it is only during the last decade that clear evidence has been obtained that inflammation plays a critical role in tumorigenesis, and some of the underlying molecular mechanisms have been elucidated (Karin et al, 2006). A role for inflammation in tumorigenesis is now generally accepted, and it has become evident that an inflammatory microenvironment is an essential component of all tumors. For over a century, the idea that the immune system can control cancer has been a subject of debate. Only very recently has it become generally accepted that the immune system has the ability not only to prevent tumor growth but also to promote it through a process called immune-editing. This process is comprised of three phases: elimination, equilibrium and escape. Elimination is achieved through identification and destruction of nascent transformed cells by acute tumor-inhibiting inflammation, characterized by infiltration of effector cells of the innate and adaptive immune system as well as production of tumor-inhibiting cytokines (Vesely et al, 2011). The most frequently found immune cells within the tumor microenvironment are tumor-associated macrophages (TAMs) and T cells. TAMs mostly promote tumor growth and may be obligatory for angiogenesis, invasion, and metastasis, and high TAM content generally correlates with poor prognosis.

Mature T cells are divided into two major groups based on the T cell receptors (TCR) they express: γδ and αβ. αβT cells are further classified according to their effector functions as CD8+ cytotoxic T cells (CTLs) and CD4+ helper T (Th) cells, which include Th1, Th2, Th17 and T regulatory (Treg) cells, as well as the natural killer T (NKT) cells. Importantly, T cells can exert both tumor suppressive and promoting effects, as determined by their effector functions. The only cells that lack a pro-tumorigenic role, so far, are NK cells. Similar to the TAMs, the tumor promoting functions of T lymphocytes are mediated by cytokines, whereas both cytokines and cytotoxic mechanisms mediate the anti-tumorigenic functions of T lymphocytes (DeNardo et al, 2009; Langowski et al, 2007).

In breast cancer, the presence of tumor infiltrating lymphocytes with high CD4+/CD8+ and Th2/Th1 ratio is indicative of poor prognosis. Th2 CD4+ T cells stimulate mammary cancer progression and metastasis by educating TAMs to produce pro-angiogenic and pro-metastatic factors (DeNardo et al, 2009). The cytokine and chemokine expression profile of the tumor microenvironment may be more relevant than its specific immune cell content. Different cytokines can either promote or inhibit tumor development and progression, regardless of their source (Lin et al, 2007). TAMs are one of the most important players in the inflammation and cancer field and an important source of cytokines (Mantovani et al, 2008). In analogy to Th1 and Th2 T cells, macrophages can be classified into M1 and M2 types. M1 macrophages, activated by IFN-γ and microbial products, express high levels of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-12 or IL-23), major histocompatibility complex (MHC) molecules and inducible nitric oxide synthase and are capable of killing pathogens and priming anti-tumor immune responses. By contrast, M2 or "alternatively" activated macrophages, which are induced in vitro by IL-4, IL-10 and IL-13, down regulate MHC class II and IL-12 expression and show increased expression of the anti-inflammatory cytokine IL-10, scavenger receptor A, and arginase. Most TAMs are considered to have an M2 phenotype while promoting tumor angiogenesis and tissue remodeling. However, most confirmed tumor-promoting cytokines are "M1 cytokines", whereas IL-10, an M2 cytokine, may be tumor suppressive (Berg et al, 1996; Lin et al, 2007). In nutshell, inflammation has been found to be involved in tumor initiation and promotion.

Cytokines in inflammation

Infection, cancer, or inflammation triggers the production of immunological mediators termed cytokines. Some cytokines clearly promote inflammation and are called pro-inflammatory cytokines, whereas other cytokines suppress the activity of pro-inflammatory cytokines and are called anti-inflammatory cytokines. For example, IL-4, IL-10, and IL-13 are potent activators of B lymphocytes. However, IL-4, IL-10, and IL-13 are also potent anti-inflammatory agents. They are anti-inflammatory cytokines by virtue of their ability to suppress genes for pro-inflammatory cytokines such as IL-1, TNF, and the chemokines. IL-1 and TNF are inducers of endothelial adhesion molecules, which are essential for the adhesion of leukocytes to the endothelial surface prior to emigration into the tissues. Taken together, pro-inflammatory cytokine mediated inflammation is a cascade of gene products usually not produced in healthy persons. The cytokines IL-1 and TNF are particularly effective in stimulating the expression of these genes. Moreover, IL-1 and TNF act synergistically in this process. Whether induced by an infection, trauma, ischemia, immune-activated T cells, or toxins, IL-1 and TNF initiate the cascade of inflammatory mediators by targeting the endothelium.

Anti-inflammatory cytokines block this process or at least suppress the intensity of the cascade. Cytokines such as IL-4, IL-10, IL-13, and transforming growth factor (TGF-β) suppress the production of IL-1, TNF, chemokines such as IL-8, and vascular adhesion molecules. Therefore, a "balance" between the effects of pro-inflammatory and anti-inflammatory cytokines is thought to determine the outcome of disease, whether in the short term or long term (Dinarello et al, 2000). All the anti-inflammatory cytokines have at least some pro-inflammatory properties as well. The net effect of any cytokine is dependent on the timing of cytokine release, the local environment in which it acts, the presence of competing or synergistic elements, cytokine receptor density, and tissue responsiveness to each cytokine. Permanent synthesis and release of these cytokines lead to increased serum cytokine concentration and act as markers of immunity status and immune system activation for prognosis and monitoring the course of cancer progression (Chopra et al, 1998).

IL-10

IL-10, initially known as cytokine synthesis inhibitory factor (CSIF), is primarily a potent anti-inflammatory Th2 cytokine that inhibits gene expression and T cell/macrophage cytokine synthesis and inhibits their antigen-presenting capacity. IL-10 is produced by monocytes and macrophages as well as Th cells dendritic cells, B cells, cytotoxic T cells, Yδ T cells, NK cells, mast cells, as well as neutrophilic and eosinophilic granulocytes (Wolk et al, 2002). It suppresses the production of IL-1α, IL-1β, TNF-α, IL-6, IL-8, IL-12, IL-18, granulocyte–macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1α (MIP-1α), RANTES (Regulated upon activation, normal T cell expressed, and secreted), leukemia inhibiting factor, and IL-10 itself. IL-10 also inhibits IFN-Y synthesis by activated Th-cells and peripheral blood mononuclear cells (PBMC) and induces mast cell proliferation (Fitzgerald et al, 2001). IL-10 is also a strong stimulator of B cell differentiation for immunoglobulin secretion. IL-10 inhibits nuclear factor κB (NF-κB) translocation considered as a mechanism for inhibiting immediate-early pro-inflammatory response (Lentsch et al, 1997). IL-10 is located on chromosome 1 and mature human IL-10 consists of 160 amino acids with molecular weight of approximately 18 kDa in monomeric form. The homodimeric protein with single transmembrane domain subunits binds to class II cytokine receptor (Kotenko et al, 1997). Human IL-10 contains four exons, which show 73% amino acid homology with murine IL-10 (Fitzgerald et al, 2001).

Inflammatory status of IL-10

IL-10 is the most important anti-inflammatory, immunoregulatory cytokine found within the human immune response. It is a potent inhibitor of Th1 cytokines, including both IL-2 and IFN-Y. This activity accounts for its initial designation as cytokine synthesis inhibition factor. In addition to its activity as a Th2 lymphocyte cytokine, IL-10 is also a potent deactivator of monocyte/macrophage pro-inflammatory cytokine synthesis (Clarke et al, 1998).

IL-10 is primarily synthesized by CD4+Th2 cells, monocytes, and B cells and circulates as a homodimer consisting of two tightly packed 160-amino-acid proteins. After engaging its high-affinity 110-kd cellular receptor, IL-10 inhibits monocyte/macrophage-derived TNF-α, IL-1, IL-6, IL-8, IL-12, granulocyte colony-stimulating factor, MIP-1α (macrophage inflammatory protein-1-alpha) and MIP-2α (Clarke et al, 1998). IL-10 inhibits cell surface expression of major histocompatibility complex class II molecules, B7 accessory molecules, and the LPS recognition and signaling molecule CD14. It also inhibits cytokine production by neutrophils and natural killer cells. IL-10 inhibits nuclear factor κB (NF-κB) nuclear translocation after LPS stimulation and promotes degradation of messenger RNA for the pro-inflammatory cytokines (Opal et al, 1998). IL-10 is readily measurable in the circulation in patients with systemic illnesses and a variety of inflammatory states. It is present in sufficient concentrations to have a physiologic impact on host responses to systemic inflammation (Marchant et al, 1994).

IL-6

IL-6 is a phosphorylated glycoprotein containing 185 amino acids. The human IL-6 gene has a length of approximately 5 kb and contains five exons and four introns. It maps to human chromosome 7p21 between the markers D7S135 and D7S370 (Bowcock et al, 1988). IL-6 is thought to increase the activity of the 17-h-hydroxysteroid dehydrogenase, which converts estrone to estradiol, a process that may contribute to the increased concentration of estrogen around breast tumors (Robinson et al, 1998). It is a pleiotropic cytokine involved in different physiologic and pathophysiologic processes such as inflammation, bone metabolism, synthesis of C-reactive protein, and carcinogenesis. It is commonly produced at local tissue sites and released into circulation in almost all situations of homeostatic perturbation typically including endotoxemia, endotoxic lung, trauma, and acute infections (Diehl et al, 2002). However, it still remains unclarified whether during local or systemic acute inflammatory responses; IL-6 is also directly involved in the modulation of other aspects of inflammation, particularly cytokine responses and tissue inflammatory infiltration. IL-6 has also been shown to inhibit the growth of various breast cancer cell lines, shows anti-adhesive effects (Badache et al, 2001), and modulates the estrogen receptor and progesterone receptor content of these cells (Danforth et al, 1993).

Inflammatory status of IL-6

IL-6 mainly produced by non-malignant cells such as T cells, B cells, monocytes and poly-morphonuclear cells (PMNs) and a number of malignant cells e.g. melanoma or renal cell carcinoma. IL-6 has long been regarded as a pro-inflammatory cytokine induced by LPS along with TNF-α and IL-1. IL-6 is often used as a marker for systemic activation of pro-inflammatory cytokines (Barton et al, 1997) like many other cytokines; IL-6 has both pro-inflammatory and anti-inflammatory properties. Although IL-6 is a potent inducer of the acute-phase protein response, it has anti-inflammatory properties as well (Barton et al, 1996). Recent evidence generated from IL-6 knockout mice has demonstrated that IL-6, like other members of the gp130 receptor ligand family, acts predominantly as an anti-inflammatory cytokine. After binding to its specific α receptor, IL-6 complexes with the ubiquitous gp130 signal transducing unit. IL-6 belongs to a family of gp130

receptor ligands that includes IL-11, leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M, and cardiotrophin-1. IL-6 down-regulates the synthesis of IL-1 and TNF by macrophages (Xing et al, 1998). IL-6 attenuates the synthesis of the pro-inflammatory cytokines while having little effect on the synthesis of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β). At the same time, IL-6 inhibits the production of pro-inflammatory cytokines such as GM-CSF, IFN-Y, and MIP-2 (Barton et al, 1997). The net result of these immunologic effects placed IL-6 among the anti-inflammatory cytokine group.

Serum level of IL-6 in breast cancer

Several studies analyzed the IL-6 levels between control and breast cancer patients and also between lower stages and higher stages of disease. Kozlowski et al (Kozlowski et al, 2003) assessed the concentration of IL-6 (and also IL-8 and IL-10) in blood serum of breast cancer patients to determine whether it correlates with the disease progression. They showed statistically higher serum concentrations of IL-6 (and IL-8 and IL-10) in breast cancer patients in comparison with healthy women, which also correlated with clinical stage of breast cancer. Yokoe et al (Yokoe et al, 2000) showed that serum IL-6 levels in progressive recurrent breast cancer patients, who did not respond the therapy, were significantly higher than the levels in recurrent breast cancer patients, who were stable after therapy. Patients whose serum IL-6 concentration was 20 pg/ml or more died within 4 months of the beginning of treatment. Jiang et al. (Jiang et al, 2000) found serum IL-6 levels were significantly higher in patients with breast cancer (38.3 ± 138.7 pg/ml) than in normal women (0.7 ± 2.5 pg/ml).

Bozcuk et al (Bozcuk et al, 2004) proposed IL-6 as an independent negative prognosticator in breast cancer patients with metastatic disease. Similar results were worked out by Saldago et al (2003). The study was designed to evaluate prospectively the independent prognostic importance of circulating IL-6 in 96 patients with untreated metastatic breast cancer, and to evaluate whether there is an association with clinic pathological variables, with tumor load and with tumor extension. The median IL-6 value for the breast cancer population was 6.6 ± 2.1 pg/ml. Patients with two or more metastatic sites had higher IL-6 values compared to those with only one metastatic site (respectively, 8.15 ± 1.7 and 3.06 ± 6.6 pg/ml).

IL-1β

IL-1β is a multifunctional pro-inflammatory cytokine, playing an important role in the pathogenesis of cancers. IL-1 is a family of three proteins IL-1α, IL-1β and IL-1Ra, which are encoded by different genes (IL-1A for IL-1α, IL-1B for IL-1β and IL-1RN for IL-1Ra), spanning a 430 kb region on chromosome 2q14 are an important component of the innate immune system. Interleukin- 1 β (IL-1β) is not only an important host genetic factor but also a key pro-inflammatory cytokine (Nicklin et al, 1994), which can regulate the expression of several molecules involved in inflammation. IL-1β is secreted primarily by macrophages but also from neutrophils, endothelial cells, smooth muscle cells, glial cells, astrocytes, B- and T-cells, fibroblasts and keratinocytes. Production of IL-1β by these different cell types occurs only in response to cellular stimulation. In addition to its effects on T-cells, IL-1β can induce proliferation in non-lymphoid cells.

IL-1β along with IL-1α and TNF are defined as 'alarm cytokines' that are secreted by macrophages to initiate inflammation. IL-1 and TNF stimulate their own and each other's production, and this represents an important amplification loop of the inflammatory response. Also, IL-1 and TNF induce adhesion molecules, such as intercellular adhesion molecule-1 that promote leukocyte infiltration from the blood into tissues. The form and quantity of IL-1, the type of the malignant cells, the tumor's stage, and the

overall local network of cytokines and their receptors, all influence malignancy (Smyth et al, 2004). IL-1β cause inflammation, but more importantly, it induces the expression of pro-inflammatory genes, such as cyclooxygenase type 2, inducible nitric oxide synthase, and other cytokines/chemokines. Pro-inflammatory cytokines may play a role in the early stages of carcinogenesis, as they induce growth factors for the premalignant cells and cause the production of reactive oxygen intermediates that are mutagenic to cells (Dinarello et al, 1996).

Jin et al. reported that IL-1β was expressed in 90% of invasive breast carcinomas and to a lesser extent in ductal in situ carcinomas and benign lesions (Jin et al, 1997). Honma et al. demonstrated that inflammatory cytokines such as IL-1β regulate proliferation of breast cancer cells through estrogen production by steroid-catalyzing enzymes in the tissue (Honma et al, 2002). IL-1 and TNF stimulate their own and each other's production, and this represents an important amplification loop of the inflammatory response. Also, IL-1 and TNF induce adhesion molecules, such as intercellular adhesion molecule-1 that promote leukocyte infiltration from the blood into tissues. The form and quantity of IL-1, the type of the malignant cells, the tumor's stage, and the overall local network of cytokines and their receptors, all influence malignancy (Smyth et al, 2004). A study conducted on breast cancer patients showed significantly elevated serum level of IL-1 β in comparison to controls (Erdei et al, 2010).

TGF-β

Friend or foe? Trustworthy guardian of normal homeostasis or double agent? Over the past two decades, the perceived role of transforming growth factor (TGF-β) in carcinogenesis has undergone a lot of twists. The initial experiments leading to the discovery of TGF-β and its naming as a "transforming" growth factor were based on its ability to induce malignant behavior of normal

fibroblasts, leading to the notion that TGF-might be a key factor in uncoupling a cell from normal growth control in such a way that it could become tumorigenic.

TGF-β is known as low penetrance genes in cancer. It is synthesized as an inactive precursor and requires activation before exerting its effect. The active molecule is a 25-kd homodimer of two 12.5-kd disulfide-linked similar structure monomers. It belongs to a super family of 20 distinct dimeric proteins that share a similar structure. There are three isoforms of TGF-β (TGF-β1, TGF-β2, and TGF-β3), of which TGF- β1 is most widely expressed. TGF-β1 gene is located on chromosome 19q13.1 (OMIM 190180) (Fujii et al, 1986). It belongs to a family of dimeric polypeptide growth factors that includes bone morphogenic proteins (BMPs) and activins (Massague et al, 1998). Practically, every cell in the body produces both TGF-β and its similar receptors. TGF-β is involved in the proliferation and differentiation of cells, embryonic development, angiogenesis, and wound healing.

TGF-β1 is a multi-functional, but mainly known as anti-inflammatory cytokine produced by cancer cells, myeloid cells, and T lymphocytes plays an important role in breast carcinogenesis (Imamura et al, 2012). TGF-β1 is a potent inhibitor of proliferation of epithelial, endothelial and hematopoietic cells, and it acts as a tumor suppressor. TGF-β1 has dual role in carcinogenesis with tumor suppressive effects in epithelial cells, but tumor invasion and metastasis promoting effects during later stages of carcinoma progression. A majority of breast cancers secrete elevated TGF-β1 in tumor micro-environment associated with either malignant epithelial cells, stromal cells or both. Increased immuno-reactivity for TGF-β protein correlates with poor prognosis and increased lymph node involvement (Ivanović et al, 2003), and elevated TGF-β associate with tamoxifen resistance .The role of TGF-β has been widely recognized in cancer stem cells (Mishra et

al, 2005) and Transforming growth factor beta (TGF-β) signaling is one of the most commonly altered cellular pathways in human cancers. Eventually, TGF-β is thought of as a potential target for management of cancer and inhibition of TGF-β has been tried for treating cancer, but without significant success till now (Yingling et al, 2004).

Inflammatory status of TGF-β

Like many cytokines, TGF-β has both pro- and anti-inflammatory effects. It functions as a biological switch, antagonizing or modifying the action of other cytokines or growth factors. The presence of other cytokines may modulate the cellular response to TGF-β, and the effect may differ depending on the activation state of the cell (Kingsley et al, 1994). TGF-β is capable of converting an active site of inflammation into one dominated by resolution and repair. TGF-β often exhibits distinct effects with immune-enhancing activity in local tissues and immune-suppressive activity in the systemic circulation. TGF-β1 suppresses the proliferation and differentiation of T cells and B cells and limits IL-2, IFN-Y, and TNF production. TGF-β1 acts as a monocyte/ macrophage deactivator in a manner similar to IL-10. However, TGF-β is less potent an inhibitor than IL-10 and has little or no effect on IL-1 production (Letterio et al, 1997). The severe and uncontrolled inflammatory reactions observed in the TGF-β1 knockout mouse attests to the physiologic role of TGF-β as an endogenous anti-inflammatory cytokine (Shull et al, 1992).

Progression to metastatic disease is generally accompanied by decreased or altered TGF-responsiveness and increased expression or activation of the TGF-β ligand. These perturbations, along with other changes in genetic or epigenetic context of the tumor cell and its stromal environment, combine to alter the spectrum of biological responses to TGF-β (Adapted from Roberts et al, 2003).

In cancer, TGF-β1 is up regulated to a greater extent than either TGF-β2 or TGF-β3 (Dickson et al, 1987) and as a result TGF-β1 has been the focus for most of the cancer related studies to date. TGF-β will often suppress early tumorigenesis and later enhance tumor progression (Derynck et al, 2001). In human cancer, many studies have demonstrated that TGF-β mis-regulation has a significant impact on tumor progression and patient prognosis. Increased serum levels of TGF-β1 associated with a mutation in theTGF-β1 gene, for example, have been associated with a lower incidence of breast cancer (Ziv et al, 2001).This correlation suggests that the TGF-β1 ligand promotes tumor suppression during the early stages of initiation and progression. Complimentary observations have shown that low levels of TGF-βR2 gene expression correlate with an increased risk of breast cancer (Gobbi et al, 1999).In contrast to the role of tumor suppression during tumor initiation and early progression, TGF-β1 may actually promote cancer progression in later stages. These combined results suggest that TGF-β is able to mediate cell autonomous, local and systemic responses that together regulate initiation, progression and prognostic outcome in human cancer.

Cell culture and xenograft methods have also been widely used to analyze the TGF-β contribution to epithelial cell autonomous regulation of tumor progression and metastasis. One of the first studies to clearly suggest a role for TGF-β during tumor progression and metastasis demonstrated enhanced invasion in vitro and metastasis in vivo after treating adenocarcinoma cells with TGF-β (Welch et al, 1990). TGF-β is clearly associated with human cancer and remains a potential target for therapeutic intervention, however at present, there are no conventional strategies in use for targeting this pathway in vivo. In order to produce a safe and effective strategy for targeting TGF-β in the regulation of human cancer, further research must be performed in mouse models to validate such strategies.

Currently, many genetic and pharmacological approaches are in use to address the regulation of cancer in mice.

TNF-α and β

The term tumor necrosis factor (TNF) refers to two closely related cytokines (encoded by separate genes) known as tumor necrosis factor-α (TNF, cachectin) and tumor necrosis factor-β (lymphotoxin, TNF-β, LTA). Both cytokines interact with the same cell membrane receptors, and both have been implicated as pathogenic mediators of human illness. TNF-β (lymphotoxin) which has close structural homology and about 30% amino acid sequence identity to TNF-α, and is recognized by the same widely distributed cellular TNF receptors. As a consequence, many of their numerous effects are similar. Tumor necrosis factor beta TNF-β is an important pro-inflammatory cytokine excreted by lymphocytes and it has both anti-tumor and pro-cancer activity. The human tumor necrosis factor (TNF) locus is located on chromosome 6p21.3 (Honchel et al, 1996). Both these genes encode proteins which have cytostatic and cytotoxic effects on certain tumors. TNF constitutes a useful immunological biomarker in breast carcinogenesis owing to its elevated levels in circulation along with enhanced TAM derived expression of TNF. This is suggestive of metastatic behavior of inflammatory breast carcinomas.

TNF-α is a pro-inflammatory cytokine involved in the growth, differentiation, cellular function, and survival of many cells and produced by diverse kinds of cells including macrophages, neutrophils, fibroblasts, keratinocytes, NK cells, T and B cells, tumor cells or inflammatory cells in the tumor microenvironment can promote tumor cell survival through the induction of genes encoding NF-kB dependent anti-apoptotic molecules (Luo et al, 2004). TNF-α has also been proposed to contribute to tumor initiation by stimulating the production of genotoxic molecules, that is, molecules that can lead to DNA damage and mutations, such as NO and ROS. Initially proposed to have anti-carcinogenic effects, TNF alpha was later shown to be tumourigenic in both in vitro and in vivo studies. Other actions of TNF-α that might enhance tumor progression, as opposed to tumor initiation, include promotion of angiogenesis and metastasis, as well as impairment of immune surveillance by strongly suppressing many T cell responses and the cytotoxic activity of activated macrophages (Elgert et al, 1998). TNF-α is a key angiogenic molecule that may facilitate angiogenesis directly by stimulating endothelial cell proliferation and indirectly by regulating expression of other pro-angiogenetic factors.

TNF-α is a multifactorial cytokine. As implied by its name, TNF-α may have cytotoxic and apoptotic activities when administered to breast tumor cell lines. However, these effects may depend on multiple factors, such as treatment by estrogen and the expression of members of the epidermal growth factor receptor family. TNF-α activity vary under different physiological conditions and in a cell-type-dependent manner contributes to a sense of ambiguity regarding its antitumor effects (Balkwill et al, 2001). In fact, recent investigations strongly suggest that the chronic expression of TNF-α in breast tumors actually supports tumor growth. The number of cells expressing TNF-α in inflammatory breast carcinoma was found to be correlated with increasing tumor grade and node involvement, and TAM-derived TNF-α expression was suggested to play a role in the metastatic behavior of breast carcinomas (Leek et al, 1998).

Serum level of TNF

Initial studies of TNF in breast cancer demonstrated that increased circulating levels of this cytokine were correlated with an increased tumor stage and lymph node metastasis. Also, levels of TNF were found to be increased in invasive breast tumor samples compared with benign tissue, specifically in the stromal compartment of the tumor. Studies of TNF action

in ER positive breast cancer cell lines have shown contrasting results. There is now convincing evidence implicating TNF-α in regulating the activities of the enzymes that are involved in estrogen synthesis and also in blocking the proliferative response of breast cancer cells to estradiol through down-regulation of ER. Furthermore, patients with more progressed tumor phenotypes were shown to have significantly higher TNF-α serum concentration (Sheen-Chen et al, 1997). Study conducted by Erdie E et al showed significantly higher level of TNF-α in breast cancer patients in comparison to controls (Erdie et al, 2010).

CONCLUSION

The cytokine and chemokine expression profile of the tumor microenvironment may be more relevant than its specific immune cell content. Different cytokines can either promote or inhibit tumor development and progression, regardless of their source. IL-10 is the most important anti-inflammatory and immunoregulatory cytokine found within the human immune response. It is a potent inhibitor of Th1 cytokines, including both IL-2 and IFN-Y. IL-6 has also been shown to inhibit the growth of various breast cancer cell lines, shows anti-adhesive effects, and modulates the estrogen receptor and progesterone receptor content of these cells. Nevertheless, the exact nature of the role of IL-6 in cancer remains unknown. IL-1β is a multifunctional pro-inflammatory cytokine, playing an important role in the pathogenesis of cancers. IL-1β along with IL-1α and TNF are defined as 'alarm cytokines' that are secreted by macrophages to initiate inflammation. IL-1β is expressed in 90% of invasive breast carcinomas and to a lesser extent in ductal in situ carcinomas and benign lesions. TGF-β1 is a multi-functional, but mainly known as anti-inflammatory cytokine produced by cancer cells, myeloid cells, and T lymphocytes plays an important role in breast carcinogenesis. It remains controversial whether this is a friend or a foe. TNF-α is a pro-inflammatory cytokine involved in the

growth, differentiation, cellular function, and survival of many cells and produced by diverse kinds of cells including macrophages, neutrophils, fibroblasts, keratinocytes, NK cells, T and B cells, tumor cells or inflammatory cells in the tumor microenvironment can promote tumor cell survival through the induction of genes encoding NF-kB dependent anti-apoptotic molecules. In nutshell, inflammation has been found to be involved in tumor initiation and promotion of cancer and cytokines play either pro- or anti-inflammatory roles in cancer with the role of some remaining dubious.

Acknowledgements

Conflict of Interest

The author declares that no competing interest exists.

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