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Cytokine regulation networks in the cancer microenvironment

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1. ABSTRACT

During carcinoma formation, cancer cells release various cytokines and growth factors into their surroundings and recruit and reprogram many other types of cells in order to establish a tumor microenvironment. Consequently, The tumor tissues almost always contain a large number of endothelial cells, fibroblasts, and infiltrating inflammatory cells that in turn produce a variety of cytokines. The cytokines produced by these cells have been posited as key factors in modulating immune response either against or in favor of tumorigenesis in the microenvironment. The interactions that take place between immune and cancer cells are complex, involving multiple cascades of cytokines, chemokines, and/or growth factors. In this review, we address the essential pro- and anti-tumorigenic roles of cytokines in the tumor microenvironment. As the interaction of cytokines, growth factors, and cancer cells forms a comprehensive network at the tumor site that is then responsible for the overall progression or rejection of the tumor, the current review links the microenvironment-derived cytokines and growth factors to a number of different kinds of human carcinogenesis models. Multifunctional cytokines, extracellular matrix mediators, and regulatory cytokines in the cancer environment are all shown to be key factors in the different cancer immune-editing systems. The characterization of cytokine networks in various types of cancer cells may yield important information for understanding the immune-related mechanisms of cancer development, and this knowledge may have subsequent application in cancer immunotherapy..

2. INTRODUCTION

The tumor microenvironment consists of a variable combination of tumor cells, stromal fibroblasts, endothelial cells, and infiltrating leukocytes, such as macrophages, as well as T lymphocytes and tumor-associated dendritic cells (TADC). In addition, eosinophils, granulocytes, natural-killer (NK) cells, and B cells are all found in some types of tumor. A variety of cytokines, chemokines, and growth factors are produced in the local tumor environment by different cells; this accounts for the complex cellular interaction and regulation of differentiation, activation, function, and survival of multiple cell types.

In comparison to normal tissues, the tumor stroma is associated with an altered extracellular matrix (ECM) and an increased number of fibroblasts that synthesize growth factors, chemokines, and adhesion molecules (1). The development and progression of cancer depends on genetic and epigenetic alterations in the transformed cells. However, many of the steps in cancer genesis---e.g., proliferation, invasion, angiogenesis, and metastasis---are promoted by such micro-environmental factors as the growth factors and proteolytic enzymes produced by stromal cells. Indeed, the reciprocal interactions between tumor and tumor stroma cells--- i.e., cancer-associated fibroblasts (CAFs), tumor endothelial cells (TECs), and tumor-associated macrophages (TAMs) - result in tumor progression (Figure 1). CAFs are reactive fibroblasts with a distinctive phenotype in contrast to the quiescent fibroblasts that are found in differentiated adult

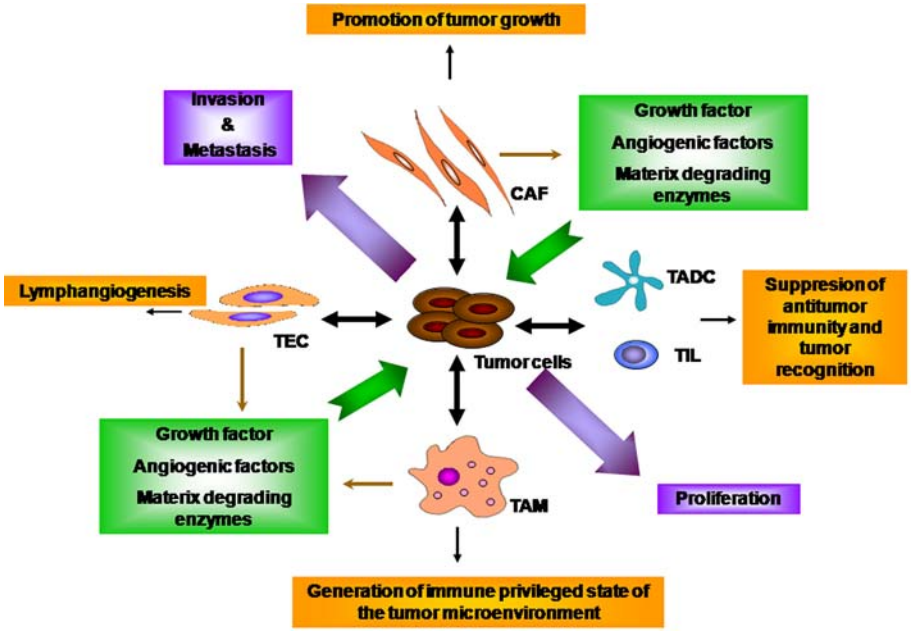

Figure 1. Interaction of the tumor microenvironment on tumor development. Cancer associated fibroblast (CAM), tumor endothelial cell (TEC), and tumor-associated macrophages (TAM) express growth factors sustaining tumor growth, angiogenic factors promoting angiogenesis, and matrix degrading enzymes catalyzing the degradation of the ECM facilitating tumor cell invasion and finally metastasis. CAF, cancer associated fibroblast; TEC, tumor endothelial cell; TAM, tumor-associated macrophages; TIL, tumor-infiltrating lymphocyte; TADC, tumor-associated dendritic cell.

tissue. CAFs stay in close vicinity of tumor cells and promote tumor growth by secreting such growth factors as transforming growth factor β (TGF-β), and matrix degrading enzymes (e.g., matrix metalloproteinases (MMPs)), as well as angiogenic factors like vascular endothelial growth factor (VEGF). TECs support the neoplastic cells by producing growth factors and are necessary for tumor hem- and lymphangiogenesis while TAMs represent a major component of the leukocyte infiltrate in solid tumors that secrete both growth factors and proteolytic enzymes. Both tumor stromal cells and their products may generate an immune-privileged state within the tumor microenvironment.

To gain entrance into the microcirculation, tumor cells must first produce various proteases and glycosidases; this enables them to degrade the connective tissue, ECM, and basement membrane components that constitute barriers against invading tumor cells (2). The expression level and activity of various proteases in human carcinoma cells are influenced by cytokines that are produced by specific tissues (3). Once tumor cells reach the parenchyma of distant organs, they must proliferate if they are to establish a metastasis. To accomplish this, metastatic cells can seize physiologic growth factors produced by the microenvironment (4). Additionally, tumor-secreted cytokines and/or growth factors can modify the local tumor microenvironment, either by modulating the immune response, inhibiting vascular cell adhesion protein expression, or inducing angiogenesis. Important components in this linkage are the cytokines produced by activated innate immune cells that stimulate tumor growth and progression. In addition, soluble mediators produced by cancer cells recruit and activate inflammatory cells and these further stimulate tumor progression. Chronic inflammation is involved in tumor initiation, promotion, and progression (5,6). Recent data from human cancer models has established that inflammation, which orchestrates the tumor microenvironment, as a critical component of tumor progression (7). Certain transcription factors that regulate the expression of many genes can suppress tumor cell death, stimulate tumor cell cycle progression, enhance epithelial-to-mesenchymal transition, and provide an inflammatory microenvironment that supports tumor invasion, angiogenesis, and metastasis (8).

During tumorigenesis, selective pressure drives tumor cells to develop several strategies for growth and propagation. Transformed cells produce or elicit factors that provide growth signals, nutrients, and a favorable tumor microenvironment. In addition, tumor cells can escape elimination by the immune system through several mechanisms. For instance, they may develop resistance to T-cell-induced apoptosis or express immune-modulatory cytokines. There are two outcomes for interactions between tumor cells and tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment: cytokines secreted by tumor and inflammatory/immune cells can either promote tumor development and tumor cell survival or they can exert antitumor effects. Chronic inflammation develops through the action of various inflammatory mediators (including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-17) leading to the eradication of antitumor immunity and the acceleration of tumor progression. Nevertheless, certain

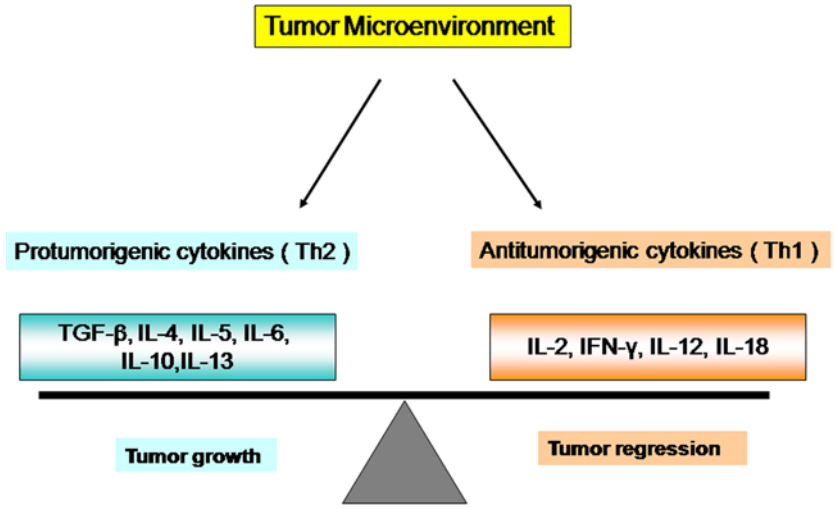

Figure 2. Role of intratumoral T cytokines in directing tumor progression versus antitumor immunity. Cytokines play a crucial role in the regulation of key pathways of immunity through the balance between cell-mediated (Th1) and humoral (Th2) responsiveness. A marked deregulation in the balance between Th1 and Th2 immune response is associated with the course of cancer. Dominant Th2-type responses as a consequence of the progressive loss of Th1-type responses are evident in tumor-bearing animals or cancer patients.

cytokines, such as TGF-β, IFN-γ, IL-2, and IL-15, are able to promote tumor suppression. The multiple actions of cytokines within the cancer environment help to explain their dual role in tumor development.

The interactions between the various cell types in the tumor microenvironment determine the effects of cytokines on tumor development and progression. Upon pathogen infection, both pro-inflammatory and anti-inflammatory cytokines are produced by activated myeloid cells. In addition to their direct effects on tumor cell growth, survival, and invasive properties, cytokines can govern the functions of TILs, T helper 1 (Th1) cells, NK cells, and regulatory T (Treg) cells, all of which infiltrate the tumor. In certain cases, cytokines may be produced by tumor cells and function in an autocrine and paracrine fashion (9).

Tumors that manage to thrive are considered to have "escaped" from this immuno-surveillance and so generate the basis for an immuno-editing or immuno-sculpturing theory (10). According to this theory, the underlying explanation for why tumors can grow without being recognized by the immune system is that they behave as immunologically normal tissue. Tumor cells emerge as normal growing cells that do not set off any danger signals that would activate the immune system; they express neither microbial immune-recognition patterns nor liberate stress signals to alarm the innate immune cells (11).

Cytokines play a crucial role in the regulation of the key pathways of immunity, namely the balance between cell-mediated (Th1) and humoral (Th2) responsiveness (Figure 2). Selective cytokines regulate the subpopulation of T lymphocytes responsible for this balance. Th1 lymphocyte cells produce both IL-2 and IFN-γ and promote cell-mediated immune responses. In addition, Th2 lymphocyte cells produce IL-4, IL-5, IL-6, IL-10, and IL-13, all of which favor B-cell activation and immunoglobulin production. Studies have demonstrated that in human models an increased level of Th2 cytokines may contribute to the escape of tumor cells from the immunosurveillance (12,13). Indeed, a Th1/Th2 imbalance is commonly seen in the serum of cancer patients and is thought to play a significant role in the insufficient induction of specific cell-mediated antitumor immunity (14).

3. MULTIFUNCTIONAL CYTOKINES IN THE TUMOR ENVIRONMENT

3.1. Dual roles of TGF-β mediate signaling networks

TGF-β signaling in the cancer environment shows significant impact on carcinoma initiation, progression, and metastasis *in vivo*. Among the members of the TGF-β family, which comprises TGF-β1, -β2 and -β3, TGF-β1 is most abundantly expressed in various pathological conditions, including chronic inflammatory diseases and cancers (15). TGF-β1 has been shown to reduce the immune response, promote angiogenesis, increase synthesis of proteolytic enzymes and stimulate ECM deposition in the tumor microenvironment.

TGF-β signaling also has been shown to regulate cancer growth through many mechanisms involving both tumor cell autonomous and host–tumor interactions. Aberrant TGF-β expression, activation, and mutation of signaling components are all critically important in human cancer models. Indeed, it has been shown that alterations of the TGF-β signaling pathway have prognostic significance for cases involving patients with prostate, breast, and colorectal carcinoma (16). Recent studies have also shown that loss of TGF-β signaling, either through the loss of type II TGFβ receptor (TβRII) in fibroblast cells or Small

Mothers Against Decapentaplegic 4 (Smad4) in T-cells, can initiate tumor growth (17).

It has been proposed that TGF-β produced by cancer cells stimulates stromal myofibroblast differentiation that in turn significantly alters the extracellular environment in favor of tumor expansion (18). Furthermore, loss of TGF-β signaling in epithelial cells has been observed to promote carcinoma formation, whereas restoring TGF-β signaling to carcinoma cells with down-regulated or mutated TGF-β RII actually suppressed tumorigenicity (19). TGF-β stimulation has also been shown to induce epithelial to mesenchymal transition (EMT) and squamous to spindle epithelial cell transition with associated enhanced cancer invasiveness (20).

TGF-β may function as a strong tumor suppressor during early carcinogenesis. The conditional knockout of TGF-β RII in fibroblasts has provided evidence to support a tumor-suppressive role for TGF-β in tumor stroma (21), though paradoxically, TGF-β signaling has also been shown to promote tumor progression. The tumor-promoting activity of TGF-β has been further demonstrated through the successful use of TGF-β inhibitors to halt tumor progression in various model systems (17). In human breast cancer, TGF-β signaling is initially inhibitory for low-grade tumors, but stimulatory for high-grade and metastasis tumors (22).

While the conditional knockout of the TGF-β type II receptor in fibroblasts (Tgfbr2FspKO) has been shown to inhibit normal mammary gland development in Tgfbr2FspKO mice, in a xenograft model it actually enhanced the growth of tumor cells (23). TGFβ2 is likely to render peripheral dendritic cells (DCs) tolerogenic, though in lymph nodes TGFβ1 may have a major impact (24). Immune cells have been reported to secrete various isoforms of TGF-β and reciprocally promote an immunosuppressive phenotype of these cells (25,26). In sum, tumor cells may escape from immune surveillance by excreting repressive cytokines, such as IL-10 and TGF-β, during tumor development (27). TGF-β1 and epidermal growth factor (EGF) have been shown to up-regulate a number of ECM enzymes, including MMPs, in epithelial cells, suggesting that TGF-β1, together with EGF families, largely regulate the morphological and invasive phases of the EMT phenotype. (28).

Bone metastasis of human breast cancer usually results in osteolytic lesions as activated osteoclasts degrade bone matrix. Growth factors released from the bone matrix promote cancer cell proliferation and contribute to what has been described as “the vicious cycle”. In particular, TGF-β and insulin growth factor-1 (IGF-1), both of which are released from the matrix during bone degradation, stimulate the production of parathyroid hormone-related protein (PTHrP) that in turn fosters cancer cell growth (29).

TGF-β is an important physiologic regulator of cell growth and differentiation. Human Cysteine-rich 61 (Cyr61), a multifunctional protein expressed by many human cancers that can stimulate angiogenesis and tumor growth transcription, can be activated by TGF-β, thus promoting the cancer metastases (30). Through the initiation of tumor-promoting paracrine interactions, numerous growth factors (including IGF-I and -II, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), bone morphogenetic proteins (BMP), and the pleiotropic cytokine TGF-β) can create a favorable bone microenvironment for tumor growth (31). TGF-β can also affect tumor growth and survival by influencing the secretion of other growth factors and the manipulation of the tumor microenvironment (32,33). Loss of extracellular TGF receptors and disruption of intracellular TGF-β signaling by oncogenes is seen in a variety of malignant and premalignant states.

3.2. TNF-α acts on multiple signaling pathways in the cancer environment

Microenvironment-derived TNF-α is linked to a variety of human carcinogenesis models (34). In cancer cells, TNF-α functions via NF-κB- and neutral sphingomyelinase-dependent pathways. Activation of NF-κB is also involved in cancer development and progression (35). NF-κB activation in microenvironment cells (such as stromal fibroblasts, endothelial cells, and infiltrating leukocytes) leads to the secretion of pro-inflammatory cytokines (including TNF-α and others) that in turn activate NF-κB in premalignant cells or tumor cells. NF-κB is activated in some of the microenvironment cells in response to pathogen-associated molecular patterns (PAMP), endogenous Toll-like receptor (TLR) ligands, and unknown ligands through TLR and other receptors. The NF-κB activation leads to the induction of genes involved in proliferation, survival, angiogenesis, and metastasis. It is important to consider the reciprocal role of NF-κB and TNF-α in the development and progression of cancers.

3.3. TRAIL acts as mediators in tumor progression

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) is a potent inducer of tumor cell death (36). Recent studies have shown that blockading of NF-κB function converts TNF-α-induced tumor growth into TRAIL-mediated tumor regression (8). In a human colon cancer model, the cancer cell line proliferated in response to lipopolysaccharide (LPS) administration but regressed when the NF-κB pathway was specifically blocked in the tumor. More important, the regression is thought to be mediated by the induction of TRAIL expressed on NK cells responding to LPS-induced IFN-α/β production (37).

TRAIL is expressed on the surface of activated immune cells and apparently functions as an immune effector molecule, mediating anti-tumor cytotoxicity and immune surveillance (38). TRAIL expression is inducible by IL-2 in liver NK (39). *In vivo*, TRAIL-sensitive tumor cells may readily become resistant by challenging interactions with TRAIL-expressing, tumor-infiltrating immune cells or stromal fibroblasts. It has been recently shown that a co-culture of pancreatic tumor cells with fibroblasts leads to the activation of NF-κB and to apoptosis resistance (40). Fibroblasts, for example, provide the necessary growth signals for survival by the secretion of proliferative factors (such as TGF-β, MMPs, and

epidermal growth factor) that play a role in cancer transformation (41). Stromal cells and fibroblasts may modulate TRAIL resistance by a secreting decoy receptor for TRAIL (42). Studies have shown that IFN-γ production by T cells with interaction on tumor stromal cells is necessary for tumor rejection (43). IFN-γ-induced expression of TRAIL and its receptors in tumor and immune cells may also lead to increased resistance of the tumor by the simultaneous activity of antiapoptotic pathways.

Hypoxic environments, often present in growing solid tumors, are known to induce the up-regulation of hypoxia-inducible factor-1α (HIF-1α). This transcription factor binds to hypoxia-response elements and induces many hypoxia-response genes (44). A hypoxic environment has been shown to induce resistance to TRAIL-induced apoptosis in human colon cancer cells (45). In pancreatic carcinoma cells, TRAIL strongly induces the expression of IL-8 and/or MMPs, followed by the increased distant metastasis of tumors *in vivo* (46).

4. FACTORS MEDIATE ECM CYTOKINES IN THE CANCER ENVIRONMENT

4.1. Hepatocyte growth factor (HGF) regulates the carcinoma invasiveness

Hepatocyte growth factor (HGF) accomplishes most of the functions of the invasive program in carcinomas (loss of adhesive junctions, motility, angiogenesis, survival/apoptosis), and may interact with other signals such as hypoxia. (47,48). HGF also regulates the expression of MMPs and the plasminogen activation system for carcinoma invasiveness. Malignant epithelial tumors grow beyond the basement membrane and invade the surrounding ECM through processes involving proteolytic degradation mediated by MMPs and the plasminogen activation system (49). In human cancers, MMP-2 and MMP-9 expression is thought to be induced by TGF-β, EGF, HGF, and TNF-α. Breast cancer cells, for example, induce stromal fibroblasts to express MMP-9 via secretion of TNF-α and TGF-β, a process modulated by HGF. Invasion of ovarian cancer cells is associated with HGF and requires p70 S6 kinase (p70S6K) -mediated MMP-9 expression (50).

HGF and hypoxia may play key roles in this intricate network of signals by influencing the angiogenic and the apoptotic processes important for tumor survival, growth, and progression (7). NF-κB and Ets-1 activated by HGF control different steps of tumor cell dissemination and homing. The Ets-1 transcription factor target genes include invasion and metastasis-related genes, such as MMPs and osteopontin.

4.2. SDF-1/CXCL12 is a potent stroma-derived chemokine in malignancies

It has been demonstrated that CXCL12 promotes tumor growth and malignancy, enhances tumor angiogenesis, participates in tumor metastasis, and contributes to immune-suppressive networks within the tumor microenvironment. Besides ovarian cancer, CXCL12 expression has been reported in many human malignancies, including breast cancer, glioblastoma, pancreatic cancer, prostate cancer, and thyroid cancer (51-55). CXCL12 expression can be regulated by hypoxia- and hormone-triggered signal pathways (56). In addition, CXCL12-dependent proliferation correlated with the activation of Extracellular signal-Regulated Kinase 1/2 (ERK1/2) and AKT pathways. Both these pathways are known to be involved with the transduction of proliferative signals in normal and tumor glial cells (57).

CXCL12/CXCR4-mediated tumor cell proliferation may be regulated through estrogen signaling. About 60% of human ovarian and breast cancers are hormone-dependent and over-express progesterone and/or estrogen receptors. Hall *et al.* has shown that CXCL12 is essential for estrogen-induced proliferation of both breast and ovarian cancers (58). CXCL12 can also regulate tumor cell apoptosis. CXCL12 activates NF-κB that in turn inhibits radiation-induced TNF-α production and tumor apoptosis (59). While high concentrations of CXCL12 are able to induce angiogenesis, studies have shown that pathological levels of CXCL12 alone do not induce vascularization *in vivo* (60); instead, CXCL12 may attract plasmacytoid DCs into the tumor environment, thus inducing neoangiogenesis through the production of IL-8 and TNF-α by DCs (61).

Hypoxia simultaneously stimulates CXCR4 expression and CXCL12 production (62). CXCL12 induces MMP synthesis in different cell types and facilitates tumor cell adhesion and colonization (63). In vivo blocking of CXCR4 has resulted in the significant inhibition of breast cancer metastasis to regional lymph nodes as well as in the lung (64).

CXCL12 also plays a pivotal role in the regulation of trafficking of normal hematopoietic stem cells (HSCs) and/or nonhematopoietic stem cells in bone marrow (65). It has been postulated that CXCL12 in the tumor microenvironment may be critical for recruiting endothelial stem cells to initiate tumor vascularization. As the cancer stem cells express CXCR4, CXCL12 may mediate cancer stem cell trafficking and metastasis to organs that highly express CXCL12, such as bone marrow, lymph nodes, liver, and lung (66). Activation of $CD4^+$ Treg cells up-regulates CXCR4 expression and enables them to migrate to the bone marrow in a CXCL12-dependent manner (67).

5. REGULATORY CYTOKINES IN THE CANCER ENVIRONMENT

5.1. IFNs mediate regulatory roles in the tumor-cytokine networks

Interferons have long been associated with the regulation of the immune response to infection, inflammation, and tumorigenesis (68). The IFN family consists of three major glycoproteins that exhibit species specificity: leukocyte-derived IFN-α, fibroblast-derived IFN-β, and immune cell-produced IFN-γ. IFN-α and IFN-β belong to type I IFN family, and IFN-γ belongs to type II IFN family. Although type I IFNs have long been known to

have antitumor effects, it has only been recently that a role in tumor immune surveillance has been described for type I IFN.

IFN-α and IFN-γ have been shown to be cytostatic to human dermal microvascular endothelial cells and to human capillary endothelial cells (69). IFN-α/β can also inhibit the endothelial cell migration step of angiogenesis (70). Moreover, IFN-α/β can affect the expression of several angiogenic factors, including bFGF, IL-8, and collagenase type IV (71). The angiogenesis within and surrounding neoplasms is caused by an imbalance between pro-angiogenic molecules. The absence of IFN-β from tumor beds is associated with robust angiogenesis (72). The correlating down-regulation of Fas and IFN-γ receptor (IFN-γR) may be one strategy that tumors use to acquire a more stable metastatic phenotype enabling them to escape from cancer immunosurveillance. Consequently, tumor escape variants that have survived CTL adoptive immunotherapy exhibit decreased expression levels of both Fas and IFN-γR in vitro and in vivo (73). In a variety of human cancer models, IFNs could modulate the expression of the angiogenic molecules (74). Furthermore, differentiated epithelial cells that are at risk of environmental exposure and cancer hazards express IFNs protein and mRNA (75).

5.2. IL-1 induce cascade of immunoregulatory cytokines and mediators

The IL-1 family consists of pleiotropic pro-inflammatory and immunoregulatory cytokines, including IL-1α, IL-1β, and the IL-1 receptor antagonist (IL-1Rα). Both IL-1β and the gene-encoding IL-1Rα have been linked to an increased risk of developing cancer, particularly gastric cancer. IL-1 is abundant at tumor sites where it can stimulate the growth and invasiveness of malignant cells (76).

The role of microenvironment-derived IL-1 in chemical carcinogenesis has been thought to be associated with the invasive potential of malignant cells (77). IL-1 and TNF-α are considered ‘‘alarm’’ pro-inflammatory cytokines that are synthesized by macrophages soon after an inflammatory insult. IL-1 and TNF-α further activate stromal cells and infiltrating leukocytes to potentiate and sustain the local inflammatory response. In several types of human cancers, local IL-1 expression by the malignant cells and/or the microenvironment has been associated with aggressive tumor growth and poor prognosis. IL-1 may induce a cascade of inflammatory mediators; this results in increased tumor angiogenesis and enhanced invasiveness, as well as tumor-mediated immunologic suppression (78).

It is intriguing that within the tumor microenvironment TLRs are expressed not only on the cells of inflammatory infiltrate, but also on tumor cells. This may be an important factor in tumor escape from immune surveillance. Attachments of ligands to TLRs lead to the activation of several genes, predominantly pro-inflammatory ones such as IL-1 and TNF-α. These immunosuppressive cytokines are thought to induce apoptosis of T lymphocytes and to inhibit the maturation of DCs (79).

5.3. IL-23 / IL-17/IL-12 are key factors in the ‘cancer immuno-editing’

IL-12 and IL-23 belong to the IL-12 family of pro-inflammatory heterodimeric cytokines (80). The antitumor activity of IL-12, inhibiting tumorigenesis and inducing regression of established tumors, has been extensively reported in mouse models of cancer. The major anti-tumor activities of IL-12 derive from its ability to promote Th1 adaptive immunity and cytotoxic T lymphocyte (CTL) responses (81). Suppressed IL-12 production and the expression levels of some surface-marker molecules can lead to impaired antigen uptake and cell motility as well as naive T cell activation (27).

IL-23-overexpressing tumors show reduced growth and metastasis consistent with the stimulation of a $CD4^+$ and $CD8^+$ memory T-cell response (82). A recent report, however, describes a role for IL-23 in promoting tumor incidence and growth (83). IL-23 signaling leads to up-regulation of MMPs, increased angiogenesis, and decreased recruitment of $CD8^+$ T cells to tumors. IL-23 may antagonize IL-12 and IFN-γ and also controls the influx and activity of anti-tumor effector lymphocytes. It has been demonstrated that IL-23 promotes a memory T-cell subset called Th17 and characterized by the production of the cytokine IL-17 (84). Both Th17 cells and IL-17 play an active role in the inflammation and autoimmune diseases of murine systems (85,86). IL-23 and IL-1 may be important for amplifying and stabilizing the Th17 phenotype in chronic inflammation (84). Th17 cells may develop from naive T cells under the influence of TGF-β and IL-6 in the tumor environment (87). IL-17 engages its receptor, resulting in the release of additional inflammatory factors; these include IL-1, IL- 6, IL-8, TNF-α, prostaglandin E2, and intercellular adhesion molecule (ICAM), as well as a number of chemokines, in the inflammatory cascades (85). Moreover, IL-17 has been shown to increase the growth of several different types of tumors (88). It has been proposed that this is due at least in part to its proangiogenic effects (89). IL-17 might be a potential contributor to the inflammatory angiogenesis via induction of proangiogenic factors (VEGF) by stromal fibroblasts (90).

IL-23 can induce several hallmarks of chronic inflammatory diseases directly, independent of IL-17 (91). The promotion of tumor growth by IL-23 is owing to the combination of a number of crucial mechanisms that involve increases in metalloproteinase activity, angiogenesis, and the abundance of inflammatory cell-derived cytokines, chemokines, VEGF, and other growth factors (89). IL-23 has been proposed as a key factor in the ‘cancer immuno-editing’ concept during tumor development (92,93).

5.4. IL-6 acts as cancer growth-promoting immunoregulatory cytokine

IL-6 is a potent pleiotropic inflammatory cytokine that acts as a key growth-promoting and anti-apoptotic factor (94). It has been suggested that IL-6 plays a pivotal role in the pathogenesis of a variety of human

cancers, including Kaposi sarcoma, multiple myeloma, Hodgkin's lymphoma, breast cancer, and colon cancer (95-98).

In a human multiple myeloma model, bone marrow stromal cells (BMSCs) and associated cytokine secretion produce a high level of IL-6 that supports osteoclastogenesis and angiogenesis (98). A complex cytokine network and BMSCs create an effective niche that supports the survival and proliferation of the myeloma cells in the bone marrow microenvironment (99,100). It has been suggested that multiple myeloma cells can stimulate the production of multiple pro-osteoclastogenic cytokines in the bone marrow environment, including IL-6, IL-1α, IL-1β, and IL-11 (101). Multiple myeloma cells can respond to various soluble mediators present in their local microenvironment, including IL-6, insulin-like growth factors (IGFs), IL-1, IL-21, stromal-derived factor-1 (SDF-1), and HGF. Cytokine/adhesion-triggered cascades can further stimulate the potential of tumor cells to invade new blood vessels (102,103). In short, IL-6 has been viewed as a major cytokine for the proliferation and survival of multiple myeloma cells.

5.5. Immune regulatory role of IL-8 within the cancer milieu

IL-8 (CXCL-8), a CXC chemokine, is produced by a variety of human carcinoma cells. In the pancreatic tumor microenvironment, IL-8 mRNA can be enhanced by TNF-α, LIF, IL-1β, IL-6, IL-8, or IFN-β, suggesting a pivotal role in the progression of cancers. It has further been proposed that local inflammation of the cancer environment facilitates tumor progression and metastasis. A variety of human cancer models illustrate the immune regulatory role of IL-8 within the cancer environment (104-106). IL-8 is a chemokine that regulates polymorphonuclear neutrophil (PMN) mobilization and activity. Upon co-culturing with melanoma cells, IL-8 is up-regulated in PMNs. Melanoma cells induce IκB-α degradation in PMNs; this indicates that NF-κB signaling is essential for IL-8 secretion in PMNs. IL-6 and IL-1β from PMN-melanoma co-cultures synergistically contribute to IκB-α degradation and IL-8 synthesis in PMNs. Melanoma cells induce PMNs to secrete IL-8 through the activation of NF-κB and suggest a model in which this interaction may promote a microenvironment favorable for metastasis. By endogenous production of IL-8 in the tumor microenvironment, PMN facilitates melanoma cell extravasation through the binding of intercellular adhesion molecule-1 (ICAM-1) on melanoma cells to β2 integrins on PMNs. In human breast cancer, the skeleton is the preferred site of metastasis. Here the osteoblasts can be induced to express increased levels of IL-6, IL-8, and monocyte chemo-attractant protein-1 (MCP-1) - cytokines known to attract, differentiate, and activate osteoclasts under the influence of breast cancer cells.

5.6. IL-10 has complex effects on tumor development

In many studies, IL-10 is described as inhibiting tumor development and progression, while in others it is illustrated as pro-tumorigenic. IL-10 can inhibit NF-κB activation and consequently, the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-12 (107). IL-10 in particular has also been shown to modulate apoptosis and suppress angiogenesis during tumor regression (43). Expression of IL-10 in mammary and ovarian carcinoma xenografts inhibits tumor growth and spread (108). IL-10 can inhibit tumor growth by down-regulating major histocompatibility complex (MHC) class I expression, leading to enhanced NK cell–mediated tumor cell lysis. It has been suggested that inhibition of the tumor stroma contributes to the antiangiogenic activity of IL-10. The ability of IL-10 to down-regulate VEGF, TNF-α, and IL-6 production may also account for its inhibitory effect on the tumor stroma (109).

The IL-10 autocrine and/or paracrine loop may be important for tumor cell proliferation and survival (110), leading to the up-regulation of anti-apoptotic genes such as B-cell lymphoma 2 (BCL-2) or BCL-XL (111). In addition, the expression of IL-10 by tumor cells is linked to the development of Burkitt lymphoma through the production of the TNF family member BAFF (B cell-activating factor of TNF family) that promotes B cell and lymphoma survival (112). In diffuse large B-cell lymphoma patients, elevation of IL-10 in the plasma has been correlated with a poor prognosis. IL-10–transfected cancer cells develop highly vascular outward tumors and in a B16-melanoma xenograft model exhibited further growth (113). In addition to the direct growth modulation of cancer cells, the ability of IL-10 to suppress adaptive immune responses has been thought to favor tumor escape from immune surveillance (114).

A pivotal role has been posited for IL-10 in the immunosuppression of cancer (115,116). Clinically, cytotoxic T cells (Tc) play a central role in cellular immunity against all human cancers. The cytotoxic potential of freshly isolated Tc in TILs is usually not expressed. Human cervical cancer cells have been shown to direct the tumor-encountered T cells toward the Th2/Tc2 polarity through IL-10- and TGF-β-mediated pathways. Moreover, cancer development is usually associated with dysregulated Treg-cell immune responses. An in vitro co-culture model simulating the tumor microenvironment by promoting the induction and expansion of IL-10+ type 1 Treg cells (Tr1) has been established. Tr1 cells are chiefly characterized by high levels of IL-10 and TGF-β production with negligible IL-4 and IFN- secretion, and their phenotype is distinct from that of CD4+CD25highFoxP3+ Treg. It has been proposed that the tumor microenvironment can promote the generation of Tr1 cells that mediate the IL-10-dependent immune suppression.

IL-10 can also alter DC functions via modulating cell surface molecules to result in impaired T-cell responses. DCs are professional antigen-presenting cells (APCs) specialized to initiate and drive T-cell immunity for performing different functions within the immune system. Immature DCs are thought to be responsible for the generation of IL-10-producing Tr1 cells. More important,

IL-10 has been proposed to inhibit the stimulatory capacity of DCs through the down-regulation of MHC class II and the co-stimulatory molecules CD80 and CD86, thus inhibiting the DC maturation and polarizing DCs to tolerogenic rather than stimulatory activity (117).

5.7. IL-2/ IL-15 mediate essential role of anti-tumor immunity

IL-2 and IL-15 share a number of important properties, including the stimulation of the T-, NK-, and B-cell proliferation/maturation (118). IL-2, mainly derived from $CD4^+$ T cells, maintains the proliferation of T cells *in vitro* while *in vivo* the existence of IL-2 is associated with the development of Treg-mediated tolerance (119).

More recently, it has been shown that IL-15 expands Tr1 cells *in vitro*. The generation and expansion of Tr1 cells depend on a mixed network of cytokines, including IL-10, IL-15, and IL-2 (120). A number of studies have demonstrated that IL-2 also functions synergistically to uphold the homeostasis of Treg cells (121). Treg cells are thought to regulate peripheral tolerance to self-Ags and have also been shown to suppress anti-tumor immunity (122). Furthermore, IL-2 and TGF-β are essential for converting and expanding naive $CD4^+CD25^-$ cells to $CD25^+Foxp3^+$ regulatory T cells (123). It has been proposed that IL-2 can reduce the spontaneous apoptosis of Treg cells (124). As a whole, the γc cytokines IL-2, IL-4, IL-7, and IL-15 exert the optimal regulatory function of human $CD4^+CD25^+$ T cells in a phosphoinositide 3-kinase (PI3K) -dependent manner .

Like Treg cells, both IL-17-secreting $CD4^+$ and $CD8^+$ T cells are kinetically inducible in a variety of human and mouse tumor microenvironments. IL-2 can not only down-regulate the $IL\text{-}17^+$ T cell differentiation in the tumor microenvironment but also up-regulate the Treg cell compartment both *in vitro* and *in vivo*; this indicates the important role of IL-2 in controlling the balance between $IL\text{-}17^+$ T cell and Treg cells (93). IL-15 may act as a paracrine factor that supports clonal proliferation in B-cell chronic lymphocytic leukemia. It has been demonstrated that IL-15 produced by metastatic colon carcinoma cells can induce hyperplasia of the mucosa adjacent to colon cancer and thus lead to angiogenesis and disease progression (125). Furthermore, the anti-apoptotic activity of IL-15 in myeloma cells has previously been demonstrated (126). IL-15 is produced by bone marrow stroma cells, endothelial cells, and fibroblasts. Stromal production of IL-15 may contribute to the proliferation of malignant cells *in vivo*, and IL-15 in turn is able to stimulate the growth of myeloma cells in a way independent of IL-6.

IL-2 is a T-cell-derived cytokine that may be produced by TILs, and it is also a potent growth factor for those T lymphocytes that bear its receptor. TILs in the tumor microenvironment can be functionally inhibited and lose the ability of clonal proliferation when the expression of IL-2 receptor α (IL-2Rα) is depressed (127). Previously, we linked the failure of IL-2 signaling to the enzymatic activity of cancer-derived MMPs (128-130). Our series studies have shown that MMPs mediate the cleavage of IL-2Rα and down-regulate the proliferative capability of cancer-encountered T cells (129). The expression of MMPs is significantly associated with gelatinolytic activity and clinical stage nodal metastasis, and cancer progression in our human cancer models (130). Both IL-2 and IL-15 elaborated by TILs and macrophages may affect the malignant behavior of human uveal melanoma, thus reducing uveal melanoma cell susceptibility to NK-cell–mediated cytolysis and cisplatin-induced apoptosis (131). Both IL-2 and IL-15 elaborate a variety of cytokines, proteases, and growth factors that can affect both tumor growth and metastasis. IL-2R expressed by some non-hematopoietic tumor cells, including human and murine cutaneous melanoma cells, can result in increased proliferation, decreased susceptibility to NK-cell-mediated cytolysis, and the increased formation of liver metastases. IL-15 protects some tumor cells from Fas-induced apoptosis (126). Moreover, cutaneous melanomas expressing both IL-15 and IL-15R mRNA have been correlated with increased malignancy (132).

Recently, we demonstrated that propositional changes of the cellular immunity correlate with the survival rate of cancer patients (133). We further illustrated that inhibitory signals can govern the cytolytic functions of CD8+ T lymphocytes upon the expression of NK cell receptors (NKRs) on TILs derived from human cervical and endometrial cancers (134-136). The intracellular perforin expression of CD8+ T cells upon the up-regulation of inhibitory NKRs was minimal, thus restraining the CD8+ T-lymphocyte cytotoxicity (134). Our strong evidence illustrates that cervical cancer cells can promote the expression of inhibitory signaling via an IL-15- and TGF-β-mediated mechanism and abrogate the antitumor cytotoxicity of TILs (134-136).

6. PROSPECT

In the present study, we examine how cytokines behave and help to create a microenvironment conducive to tumor cell survival and growth (Figure 3). We discuss how cytokines affect proliferation, invasion, metastasis, and apoptosis in various types of cancer cells. We also analyze the roles of the microenvironment on tumor growth, with particular emphasis on interactions within the cytokine system. The tumor microenvironment represents a complex system in which individual immune cells make potentially interconnected decisions to attack tumor cells, ignore their presence, or alternatively, enhance their development and/or survival. Tumor cells naturally secrete pro-inflammatory cytokines and chemokines to interact with the microenvironment and regulate neoangiogenesis. In studies of various types of tumors, cytokines have been shown to be important in influencing cancer cell behavior because of the pleiotropic and overlapping nature of cytokine functions. Findings for designing effective immunotherapies for cancer patients have greatly advanced. For example, recent data shows that the anti-TGF-β1 effect of IL-6 restores the ability of IFN-γ to promote MHC class I and II antigen, formerly inhibited by TGF-β1, driving the tumor toward regression (137). It was

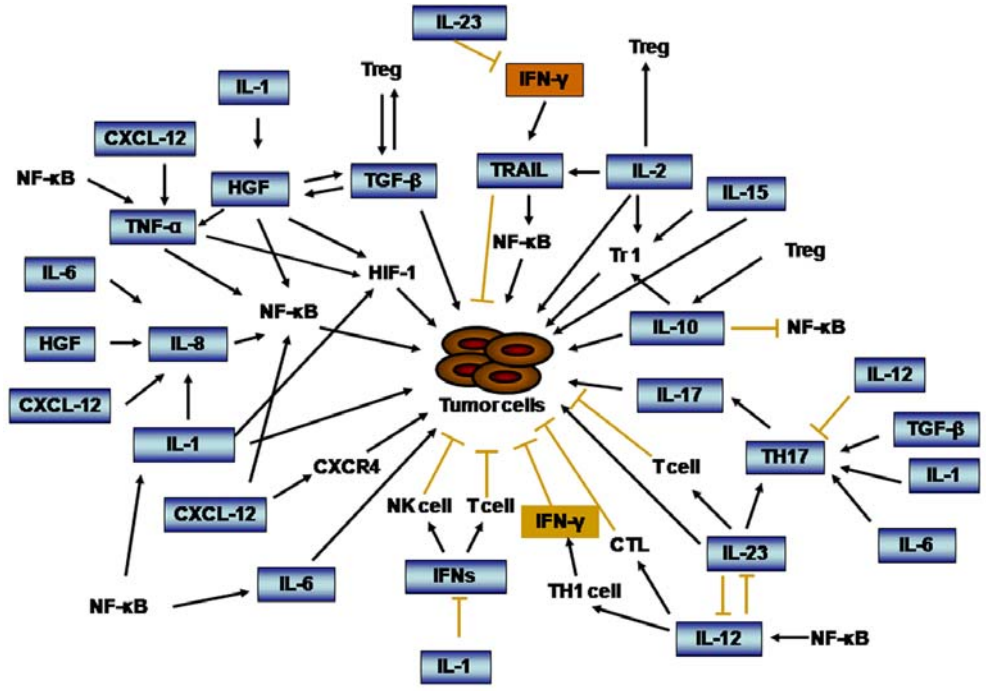

Figure 3. Pro- and anti-tumorigenic properties of cytokines in the tumor microenvironment. Cytokine regulation networks in the tumor microenvironment are complicated cascades. Cytokines secreted by tumor and inflammatory/immune cells can either promote tumor development and tumor cell survival or exert anti-tumor effects.

found that IL-2 can enhance the maturation of naïve $CD8^+$ T cells into granzyme B and CD44 expressing effector $CD8^+$ T cells and acquisition of a cytolytic $CD8^+$ T cell (138). Besides, the anticancer activity of oncolytic adenovirus vector armed with IFN-α and Adenovirus Death Protein (ADP) is enhanced by pharmacologically controlled expression of TRAIL (139). The findings in this *in vivo* tumor regression model have the potential for application in cancer immunotherapy. The possibility of cytokine regulation within the tumor microenvironment holds great promise for positive impact in the clinical setting. For now it constitutes a significant area of exploration that beckons future research.

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Abbreviations: tumor-associated dendritic cells (TADC); natural-killer (NK) cells; extracellular matrix (ECM); cancer-associated fibroblasts (CAFs); tumor endothelial cells (TECs); tumor-associated macrophages (TAMs); transforming growth factor β (TGF-β); matrix metalloproteinases (MMPs); vascular endothelial growth factor (VEGF); epithelial to mesenchymal transition (EMT); tumor infiltrating lymphocytes (TILs); tumor necrosis factor (TNF)-α; interleukin (IL); Interferons (IFN); regulatory T (Treg) cells; T helper (Th); cell-mediated (Th1); humoral (Th2); type II TGFβ receptor (TβRII); Small Mothers Against Decapentaplegic (Smad); knockout of the TGF-β type II receptor in fibroblasts (Tgfbr2FspKO); dendritic cells (DCs); epidermal growth factor (EGF); insulin growth factors (IGFs); parathyroid hormone-related protein (PTHrP); Cysteine-rich 61 (Cyr61); fibroblast growth factor (FGF); platelet derived growth factor (PDGF); bone morphogenetic proteins (BMP); nuclear factor-κB (NF-κB); pathogen-associated molecular patterns (PAMP); Toll-like receptor (TLR); tumor necrosis factor–related apoptosis-inducing ligand (TRAIL); lipopolysaccharide (LPS); hypoxia-inducible factor-1α (HIF-1α); hepatocyte growth factor (HGF); p70 S6 kinase (p70S6K); chemokine stroma-derived factor (SDF-1/CXCL12); Extracellular signal-Regulated Kinase 1/2 (ERK1/2); hematopoietic stem cells (HSCs); Cluster of Differentiation (CD); IFN-γ receptor (IFN-γR); IL-1 receptor antagonist (IL-1Rα); cytotoxic T lymphocyte (CTL); intercellular adhesion molecule-1 (ICAM-1); bone marrow stromal cells (BMSCs); polymorphonuclear neutrophil (PMN); monocyte chemo-attractant protein-1 (MCP-1); major histocompatibility complex (MHC); B-cell lymphoma 2 (BCL-2); B cell-activating factor of TNF family (BAFF); cytotoxic T cells (Tc); type 1 Treg cells (Tr1); antigen-presenting cells (APCs); common γ chain (γc); phosphoinositide 3-kinase (PI3K); IL-2 receptor α (IL-2Rα); NK cell receptors (NKRs); Adenovirus Death Protein (ADP).

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