J Clin Immunol (2013) 33 (Suppl 1):S79–S84
DOI 10.1007/s10875-012-9847-0

Cancer-Related Inflammation

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Received: 4 July 2012 / Accepted: 30 November 2012 / Published online: 9 December 2012

Abstract Solid tumors consist of neoplastic cells, non-malignant stromal cells, and migratory hematopoietic cells. Complex interactions between the cell types in this microenvironment regulate tumor growth, progression, metastasis, and angiogenesis. The cells and mediators of inflammation form a major part of the epithelial tumor microenvironment. In some cancers, inflammatory conditions precede development of malignancy; in others, oncogenic change drives a tumor-promoting inflammatory milieu. Whatever its origin, this "smoldering" inflammation aids proliferation and survival of malignant cells, stimulates angiogenesis and metastasis, subverts adaptive immunity, and alters response to hormones and chemotherapy. Cytokines are major mediators of communication between cells in the inflammatory tumor microenvironment. It is known that neoplastic cells often over-express proinflammatory mediators including proteases, eicosanoids, cytokines, and chemokines. Several cytokines such as macrophage migratory inhibitory factor (MIF), TNF-α, IL-6, IL-17, IL-12, IL-23, IL-10, and TGF-β have been linked with both experimental and human cancers and can either promote or inhibit tumor development. MIF is a major cytokine in many cancers and there is evidence that the cytokine is produced by both malignant cells and infiltrating leukocytes. In this article we will discuss the role of cancer-associated inflammation and the particular role of MIF in malignant disease.

Keywords Cytokines · cancer · malignant disease · inflammation · MIF · tumorigenesis

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Introduction

Cytokines are mediators that regulate a broad range of processes involved in the pathogenesis of cancer. Inflammation is key to the integrity and survival of multicellular organisms, but deregulation of this powerful component of the immune system is a characteristic of much chronic pathology, including cancer [1, 2]. Inflammatory processes can promote, or maybe even initiate, malignant disease [3–6].

Cancer and Inflammation

Cancer-related inflammation is an essential process in malignant disease, with common and defined players at different stages of progression [3, 7]. Until recently, the field has been driven by the hypothesis that extrinsic inflammatory pathways promote or, in some cases, initiate cancer—i.e., that inflammation causes or promotes cancer [1] (Table I). However there is now evidence that there is an intrinsic inflammation pathway activated by genetic events that cause neoplasia; i.e., cancer causes inflammation [7–13]. Activation of oncogenes such as *myc*, *ras*, and *ret*, or inactivation of tumor suppressors such as pVHL, leads to constitutive production of inflammatory cytokines by the initiated cell. Oncogene and tumor suppressor pathways are proven intracellular targets for therapies, but these recent data mean that inflammatory cytokines and their receptors are druggable extracellular targets of the genetic changes in malignant disease. The cells and mediators of inflammation also form a major part of the tumor microenvironment (Fig. 1). In some cancers, inflammatory conditions precede development of malignancy; in others, oncogenic changes drive a tumor-promoting inflammatory milieu Whatever its origin, this "smoldering" inflammation aids proliferation and survival of malignant cells, angiogenesis, and metastasis; subverts

Table I The association between inflammation and cancer in different organ systems

System	Inflammation
Respiratory	Asbestos and mesothelioma
	Silica, cigarette smoke and bronchial cancer
	Chronic asthma and bronchial cancer
Genitourinary	Human papilloma virus and penile carcinoma
	Schistosomiasis and bladder cancer
Reproductive	Pelvic inflammatory disease, ovarian epithelial inflammation and ovarian cancer
Gastrointestinal	Epstein-Barr virus and nasopharyngeal cancer
	Barrett's metaplasia and esophageal cancer
	H. pylori gastritis and gastric cancer
	Chronic pancreatitis and pancreatic cancer
	Chronic cholecystitis and gallbladder cancer
	Hepatitis and hepatocellular cancer
	Inflammatory bowel disease and colorectal cancer
	Human papilloma virus and anogenital cancer
Hematopoietic	Epstein-Barr virus and Burkitt's lymphoma
	HTLV1 and T cell leukemia/lymphoma

adaptive immunity; and alters response to hormones and chemotherapeutic agents [14, 15]. The cytokine network is of great importance in the processes of cancer-related inflammation, regulating both host and malignant cells in the tumor microenvironment [16]. The epidemiological data available are impressive and show a clear association between chronic inflammatory conditions and subsequent malignant transformation in the inflamed tissue.

Cytokines in Inflammation and Cancer

It is known that neoplastic cells often over-express proinflammatory mediators, including proteases, ecosanoids, cytokines, and chemokines. Several cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-17, IL-12, IL-23, IL-10, transforming growth factor (TGF)-β, and macrophage migration inhibitory factor (MIF) have been linked with both experimental and human cancers and can either promote or inhibit tumor development (Table II). Here we will describe some of the cytokines that may be potential targets for cancer therapy.

TNF-α is the prototypical proinflammatory cytokine. The critical role of TNF-α in chronic inflammatory diseases is well known [36]. Although originally shown to be toxic to tumor cells in high doses, the tumor-promoting function of TNF-α has been clearly demonstrated in mice [37]. Malignant cells or inflammatory cells in the tumor microenvironment can produce TNF-α, and TNF-α signaling can promote cell survival, invasion, and angiogenesis [38]. In mesothelioma, phagocytosis of asbestos fibers by myeloid cells leads to TNF-α secretion that promotes cell survival and thereby reduces asbestos-induced cytotoxicity [13]. TNF-α has also been shown to contribute to tumor initiation by stimulation of genotoxic reactive nitrogen (RNS) and oxygen (ROS) species [39]. Genetic polymorphisms that enhance TNF-α production are associated with increased risk of multiple myeloma (MM), bladder cancer, hepatocellular carcinoma (HCC), gastric cancer, and breast cancer, as well as poor prognosis in various hematological malignancies [40]. Other actions of TNF-α that may promote tumorigenesis include angiogenesis, impairment of immune surveillance through T-cell suppression, and inhibition of the cytotoxic activity of activated macrophages [41].

TNF-α binds to 2 receptors—the ubiquitously expressed TNFR1 and TNFR2, which is restricted to expression on hematopoietic cells. Previous studies show that TNFR1 is important in tumor promotion [42]. TNFR1 knockout mice are resistant to skin carcinogenesis [44] and experimental lung metastases in the renal cancer (RENCA) model [43]. Experimental liver metastases were attenuated in TNFR1-deficient mice [44]. In chimeric mice whose bone marrow

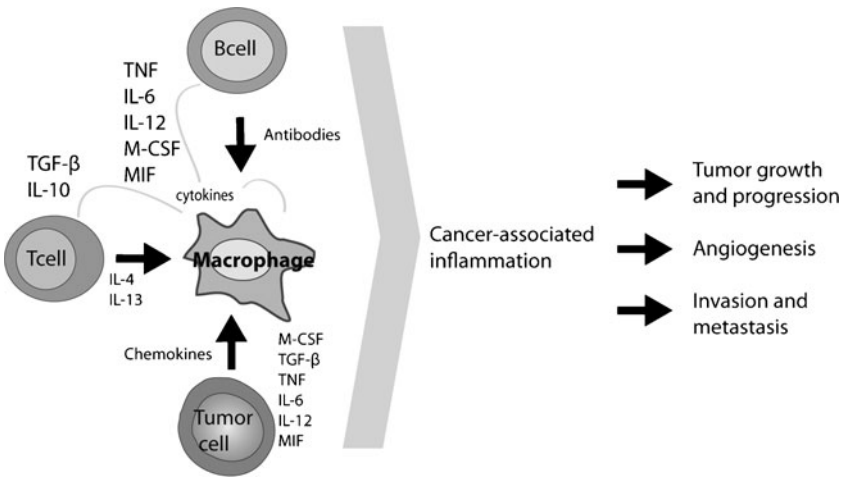

Fig. 1 Simplified overview of the interaction of cytokines in the tumour microenvironment. Several cell types contribute by producing these cytokines and their action will unfold on the surrounding cells. As a net result the cytosine milieu contributes to promotion of several key hallmarks of cancer, tumour growth and progression, angiogenesis and invasion/metastasis

Table II Cancer-associated cytokines

Target	Disease
TNF-α	Ovarian cancer [17], pancreatic cancer [18]
IL-4	Lung cancer [19]
	Breast cancer [20]
IL-6	Pancreatic cancer [21, 22]
	Breast cancer [23]
IL-11	Gastric cancer [24]
	Breast cancer [25]
	Pancreatic cancer
IL-13	Ovarian cancer [26]
	Head and neck [27]
	Glioma [28]
IL-17	Ovarian cancer [17] [29]
	Bladder cancer [30]
	Melanoma [30]
	Colon Cancer [31]
MIF	CLL [32]
	Breast cancer [33]
	Colon cancer [34]
	Prostate cancer [35]

was repopulated with TNFR1−/− cells, development of colitis and colon cancer was attenuated [45]. Several studies have demonstrated that stromal cell TNF-α is tumor promoting. In a genetic model, bone marrow cell TNF-α was implicated in promotion of inflammation-associated liver tumors [6]. In a model where chemical damage led to liver cancer, Kupffer cell TNF-α was one of the mitogens driving proliferation of genetically damaged hepatocytes [46]. In a chemically induced model of colitis and colorectal cancer, mononuclear cell TNF-α was implicated in inflammation and subsequent tumor development [45]. Several studies have reported therapeutic activity of anti-TNF-α antibodies, or a TNF receptor fusion molecule, in genetic models of liver and colorectal cancer [6, 47]; a carcinogen-induced model of colorectal cancer [45]; and pancreatic cancer xenografts [48]—although the exact mechanisms of action are not understood.

In many different experimental and human cancers, malignant cells produce TNF-α during tumor growth and spread [10, 37, 38, 48–53]. Preclinical experiments with TNF-α antagonists and early-phase clinical trials of TNF-α antagonists in patients with advanced cancer suggest that this inflammatory cytokine may be a useful target [49, 54–56].

IL-6, a pleiotropic inflammatory cytokine, is considered a key growth factor for both malignant and immune cells. Most IL-6 target genes are involved in cell cycle progression and suppression of apoptosis, which underscores the importance of IL-6 in cell survival and tumorigenesis. IL-6 is suggested to have a pivotal role in the pathogenesis of Castleman's disease [57] and MM [58]. Clear evidence that IL-6 governs the growth of MM, a malignant disorder of plasma cells, has come from studies using IL-6 knockout mice, which were found to be resistant to plasmacytoma induction [58]. In MM, stromal cells in the bone marrow produce IL-6. Its synthesis by these cells can be further enhanced by their interaction with malignant plasma cells. New IL-6 antagonists such as small molecules and monoclonal antibodies are being evaluated for treatment of MM. IL-6 is also a key mediator of inflammatory disease. IBD and colitis are associated with high concentrations of IL-6 [59]. In experimental models of colitis-associated colon cancer (CAC), HCC IL-6 production by myeloid cells is also critical for carcinogenesis [4, 60, 61].

IL-10 is an immunosuppressive and anti-inflammatory cytokine also linked with inflammation-associated cancer [7]. IL-10–deficient mice develop spontaneous colitis due to hyperactivation of immune cells, and eventually they develop CAC. Expression of IL-10 by tumor cells and macrophages is thought to promote the development of Burkitt's lymphoma through the production of the TNF family member B-cell activating factor (BAFF), which promotes B-cell and lymphoma survival [62]. An elevated amount of IL-10 in the plasma has been correlated with poor prognosis in diffuse large B-cell lymphoma patients [63]. In addition to direct growth modulation of malignant cells, the ability of IL-10 to suppress adaptive immune responses has been suggested to favor tumor escape from immune surveillance [64]. Therefore, IL-10 has complex effects on tumor development. In some experimental systems, IL-10 is found to exert antitumor activity, while in other cases it can promote tumorigenesis.

MIF was one of the first cytokine activities to be described [65, 66], originally being identified as a product of activated T lymphocytes that inhibited the random migration of cultured macrophages. It is now clear that MIF is a key regulator of immune and inflammatory responses and is produced by a range of cells and tissues. Subsequent studies of MIF

Table III Mode of action for MIF in tumor development and progression

Function	Role for development and progression
P53 inhibition	Tumour heterogeneity [85]
	Inhibition of apoptosis [78]
	Promotion of proliferation [86]
MAPK activation	Invasion [79]
	Block of apoptosis [79]
	Chemoresistance [86]
	Pro-angiogenic [34]
COX2 pathway	Direct tumor growth promotion
	Invasion and metastasis [79]
	Pro-angiogenic [34]
Immune escape	MDSC maintenance [86]
	T cell inhibition [87]

expression in vivo have established an important role in host response to endotoxic shock [67] and the inflammatory pathologies responsible for arthritis [68]. MIF is a key inducer of inflammatory cytokines such as TNF-α and IL-1 [67], and macrophages from MIF knockout mice have a severely diminished TNF-α response to bacterial endotoxin both in vitro and in vivo [69]. Recent studies describe the existence of a MIF-glucocorticoid counter-regulatory system that controls inflammation and immune response [70], and released MIF can supersede the glucocorticoid immunosuppressive effects [71]. MIF binds to the extracellular domain of CD74—the cell-surface form of the MHC class-II-associated invariant chain [72]—but needs CD44 as an integral member of the CD74 receptor complex leading to MIF signal transduction [73].

MIF expression is increased during the evolution of several malignancies [74]. MIF also has been implicated in the angiogenic switch of early cancer [75]. We reported earlier a role for MIF in macrophage-induced ovarian cancer cell invasiveness [76] in vitro and demonstrated that the inhibition of ovarian cancer-cell-derived MIF expression by MIF siRNA inhibits tumor growth, progression, and neo-angiogenesis, while increasing survival rates [77]. MIF also has the ability to protect tumor cells from apoptosis [77, 78]. Recently, Bernhagen et al. [79] showed for the first time that MIF is a potential ligand for the chemokine receptors CXCR2 and CXCR4, both of which have been shown to play a major role in ovarian cancer [38, 80–84]. Table III provides an overview of the mode of action for MIF.

The role of inflammation in tumor development is likely to depend on the nature of the tumor and inflammatory cell interaction. While inflammatory cells may produce growth factors for tumor cells, in turn the tumor microenvironment may provide factors that suppress antitumor immune responses. Identifying the mechanisms by which inflammation is deregulated in cancer and provides tumor-promoting signals may offer new therapeutic opportunities in cancer therapy. One caveat for cytokines as targets in cancer therapy: although inflammation is clearly linked with tumorigenesis, both the innate and adaptive immune systems have the capacity to recognize and eliminate malignant cells [88, 89]. Many proinflammatory cytokines may function in tumor immune surveillance, and it is vital to determine whether this mechanism offers potential as a therapeutic target.

Conflicts of interest The authors declare that they have no conflict of interest.

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