

Subversion and Coercion: The Art of Redirecting Tumor Immune Surveillance

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Abstract Tumor immune surveillance and CD8+ T cells in particular appear capable of recognizing the antigenic properties of human tumor cells. However, those antigen specific T cells are often excluded from tumor tissue or are functionally limited in their cytotoxic capacity. Instead, the immune response provides proinflammatory cytokines and proteases promoting tumor growth and progression while subverting cytotoxic anti-tumor immunity. The cytokines and the inflammatory mechanisms driving tumor associated inflammation resemble tissue remodeling processes during wound healing and chronic inflammatory diseases. In this chapter, we summarize the current knowledge of how inflammatory cytokines may promote the deviation of anti-tumor immunity toward a tumor promoting, noncytotoxic inflammation.

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1 Introduction

After decades of research, it has become clear that the human immune system recognizes the antigenic profile of tumors and amplifies tumor specific T and B cell populations (Jager et al. 2003; Van Der Bruggen et al. 2002). While cytotoxic T cells directly recognize the antigenic properties of human tumor cells (Knuth et al. 1984; van der Bruggen et al. 1991), their infiltration into tumor tissue is very limited. The presence of IFN- γ + CD8+ T cells correlates with an improved patient prognosis (Galon et al. 2006; Naito et al. 1998). Antigen presentation to CD8+ T cells is also negatively regulated in tumors, and major histocompatibility complex (MHC) molecules are expressed at low levels in the majority of cancers (Seliger et al. 2002). Moreover, low expression MHC molecules have been correlated with reduced survival of cancer patients (Han et al. 2008). However, human tumors occur more often in sites of chronic inflammation, and the chronic use of nonsteroidal anti inflammatory drugs conveys a lower incidence of cancer (Coussens and Werb 2002; Koehne and Dubois 2004; Lin and Karin 2007). In addition, survival of cancer patients appears to be negatively associated with an abundance of immune stimulatory and proinflammatory cytokines in systemic circulation. The significant upregulation of proinflammatory cytokines is particularly evident during tumor cachexia and metastasis associated with late stage cancer (Balkwill et al. 2005; Loberg et al. 2007) (Fig. 1). These data raise the question whether the failure of the adaptive immune system to eliminate disseminated tumor burden in late stage cancer patients is caused by a failure to mount the right type of response rather

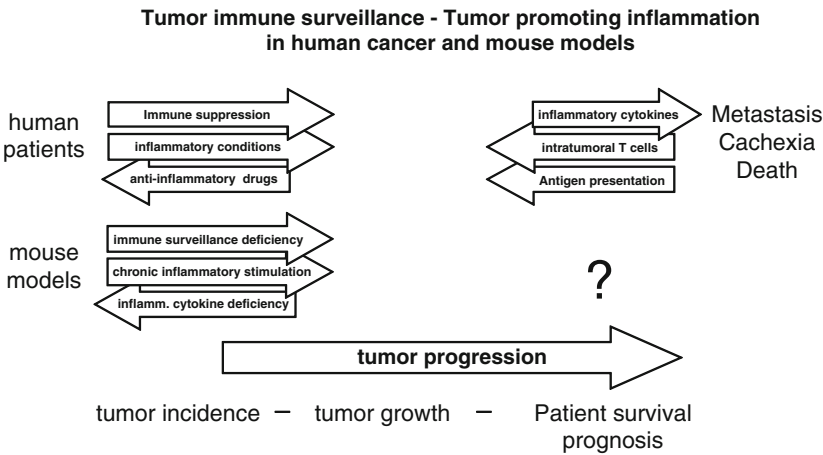


Fig. 1 *The polarization of the immune response control cancer incidence and death.* Chronic tissue damage and inflammation is not only associated with tumor incidence in human patients and mouse models but cytokines triggering inflammation are also predictors of a decreased life expectancy in human cancer patients. In sharp contrast, presence of mediators of the adaptive immune surveillance – CD8+ T cells and antigen presenting molecules – convey a favorable prognosis to cancer patients and control tumor incidence in mice and men

than a failure to detect the antigenic properties of the tumor. More specifically, do cancer patients suffer from a misguided immune response against their cancer cells, dominated by systemic immune stimulatory and proinflammatory cytokines that inhibit the intratumoral cytotoxic-immune response?

We have recently reported that the very regulation of tissue regenerating inflammation might directly inhibit the ability of cytotoxic T cell to destroy tumor cells within the inflamed tissue (Langowski et al. 2007). As a consequence, immune surveillance against tumors is largely prevented in the local microenvironment by proinflammatory mediators such as IL-23 (Langowski et al. 2006).

As described above, a solid body of evidence associates chronic inflammation with increased tumor incidence. Additionally, clinical and experimental findings also show to the up-regulation of proinflammatory molecules during tumor progression, particularly during late stages of cancer progression and during tumor cachexia (Balkwill et al. 2005). The same cytokines upregulated in tumor promoting inflammation are essential for the development of proinflammatory CD4+ and CD8+ T cells, essential for inflammatory diseases.

We outline the players in the tumor centric cytokine network and describe their simultaneous influence on effector cells of the tumor-associated inflammatory responses and on tumor immune surveillance (Fig. 2).

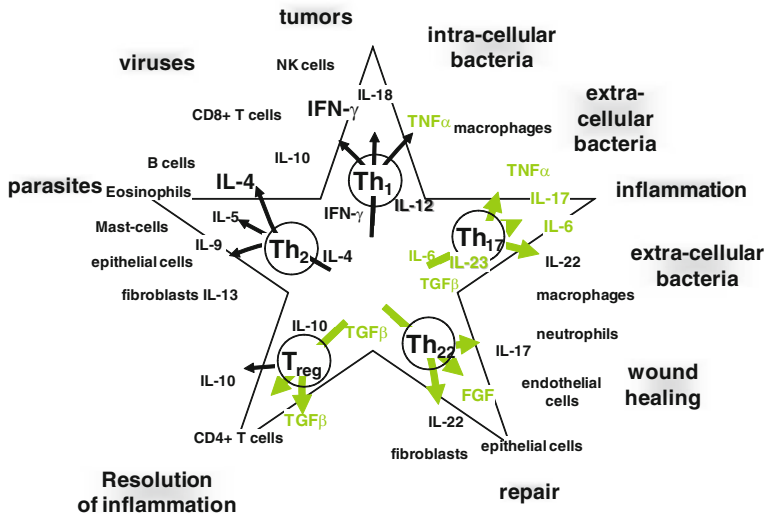


Fig. 2 Pathogen centered polarization of the adaptive immune system. To overcome multiple challenges the mammalian immune system has evolved mechanism to activate different effector populations. Closing a wound typically requires antibacterial effectors, myeloid and stromal cells, but not primarily the adaptive or cytotoxic responses required for anti-viral mechanisms. The immune response to tumors often replicates wound healing like immune reactions, inherently less capable of eliminating malignant cells. *Green*: Cytokines activated in human cancer tumors, associated with decreased prognosis or short survival of human patients. *Circle*: polarized CD4+ T cells

2 The Inflammatory Trio: TNF- α , TGF- β , IL-6

TNF- α is an essential effector cytokine for the initiation and maintenance of chronic inflammation as shown in mouse models of immune mediated disorders such as rheumatoid arthritis (Williams et al. 2000). The relevance of the TNF- α pathway for human disease is best exemplified in the success of anti-TNF- α therapies in inflammatory diseases (Feldmann and Maini 2001). Elevated concentrations of TNF- α are also found in the serum of cancer patients and correlate with a poor patient prognosis (Szlosarek and Balkwill 2003). TNF- α is closely associated with metastasis, tumor induced cachexia, an inflammation mediated multiorgan failure in late stage cancer patients and inflammatory paraneoplastic syndromes (Loberg et al. 2007). Genetic polymorphisms conferring higher TNF- α production are associated with increased risk of a variety of human cancers (Szlosarek et al. 2006).

In providing inhibitory and stimulatory signals to tumor growth, TNF- α exemplifies the conundrum of the inflammatory cytokine milieu within the tumor microenvironment. TNF- α is produced by Th1 and Th17 CD4+ T cells and macrophages. TNF- α promotes the maturation of dendritic cells but also inhibits the expression of type I interferons (Caux et al. 1992; Palucka et al. 2005; Zhou and Tedder 1996). Induction of high local concentrations of TNF- α promote tumor vascular destabilization (Lejeune et al. 1998; Ruegg et al. 1999) leading to tumor cell necrosis and tumor antigen uptake by tumor resident or associated macrophages. However, human tumors upregulate inhibitors of apoptosis (LaCasse et al. 2008), possibly to acquire resistance to the abundance of intra-tumoral TNF- α .

Conversely, TNF- α produced by tumor cells or inflammatory cells may promote tumor survival via the induction of anti-apoptotic genes controlled by NF- κ B activation. Indeed, TNF- α has been demonstrated to promote tumorigenesis as TNF- α deficient mice or mice treated with anti-TNF- α antibodies are largely protected from the chemical induction of skin papillomas (Moore et al. 1999; Scott et al. 2003). TNF- α $-/-$ mice are also very proficient at rejecting syngeneic murine tumor models implanted orthotopically (Mumm and Oft unpublished). By fostering the production of genotoxic reactive oxygen species and nitric oxide, TNF- α may also directly increase the mutation rate in tumors (Szlosarek et al. 2006). In addition TNF- α also plays a role in the truncation of an adaptive immune response. Through regulation of Fas/FasL, TNF- α can drive activation induced cell death (Elzey et al. 2001). TNF- α may therefore induce apoptosis of activated tumor infiltrating T cells, thereby blunting adaptive immune surveillance against tumors from within the tumor itself.

While the pro-apoptotic effects of TNF- α spiked interest in its therapeutic utility, the concentrations necessary to achieve therapeutic response are too high (Mocellin et al. 2005). Moreover, elevated TNF- α levels in the serum associate with a poor prognosis of cancer patients which suggests that the microenvironment of the tumor is already desensitized to high intra-tumoral levels of TNF- α . Attempting to increase the TNF- α level further may be deleterious to the host rather than eliciting

a de novo immune response. Most endogenous mouse tumor models and clinical studies indeed underline the pro-neoplastic functions of TNF- α rather than its pro-apoptotic functions on tumor cells.

Another key regulator of inflammatory processes tightly associated with chronic inflammation and cancer is transforming the growth factor β (TGF- β). TGF- β contributes to tumorigenesis by local suppression of the immune surveillance, in particular of antigen specific cytotoxic CD8+ T cells. Only recently it became clear that TGF- β is equally important for proinflammatory CD4 T cells (see below).

TGF- β inhibits the maturation, antigen presentation and costimulation by both macrophages and dendritic cells (Li et al. 2006). Immature dendritic cells produce large amounts of TGF- β and might efficiently prime regulatory CD4+ T cells (Treg). TGF- β is required for the development of Tregs and TGF- β expression by Tregs is essential for their proliferation and function. Regulatory T cells are found in human tumors and their presence correlates again with a poorer prognosis (Curiel et al. 2004). TGF- β also plays a role in the development of the proinflammatory murine IL-17 producing Th17 which share a common path with regulatory T cells.

Similar to helper T cells, TGF- β inhibits the proliferation and differentiation of CD8+ cytotoxic T cells. (Wrzesinski et al. 2007). TGF- β inhibits the expression of Interferon- γ (IFN- γ), the cytotoxic effector molecule Perforin, and the exocytosis of the cytotoxic granules (Li et al. 2006). Moreover, CD8+ T cells stimulated with both IL-6 and TGF- β , cease expression of IFN- γ , lose their cytotoxicity and secrete IL-17 (Liu et al. 2007). IFN- γ induces major histocompatibility complex (MHC I) in both dendritic cells and tumor cells. Replacing intratumoral IFN- γ expressing T cells by Th17 might severely compromise tumor immune recognition and surveillance.

IL-6 activates STAT3 and induces survival and proliferation of tumor cells in numerous experimental systems (Aggarwal et al. 2006; Naugler and Karin 2008; Rose-John et al. 2006). IL-6R α is highly expressed on tumor cells, and soluble sIL-6R α stimulates trans-signaling in cells not expressing IL-6R α (Becker et al. 2004; Rose-John et al. 2006). IL-6 protects tumor cells from apoptosis and serves as an autocrine growth factor (Baffet et al. 1991). IL-6 is also essential in the initiation and maintenance of chronic inflammation of the colon (Atreya et al. 2000) and the development of inflammation induced colon tumors (Becker et al. 2004).

IL-6 levels are typically elevated in the serum and tissue of cancer patients and correlate with a negative prognosis (Smith et al. 2001). Increased IL-6 expression due to IL-6 promoter polymorphisms may be a cancer predisposing genetic risk factor in colon cancer patients (Landi et al. 2003).

Recently, however, it has become clear that IL-6 acts with TGF- β , which is crucial to induce the IL-17 producing Th17 helper cell lineages (Mangan et al. 2006; Wilson et al. 2007). It remains to be tested how many of the effects of IL-6 in the regulation of tissue inflammation and cancer are dependent on the induction and subsequent control of this T cell lineage. Importantly, it has been shown that the proinflammatory T helper cells continue to express both IL-17 and IL-6 (Becker et al. 2004; Langrish et al. 2005).

3 The Local Trigger: IL-23 and IL-12 Balance in the Tumor Microenvironment

IL-12 and IL-23 are heterodimeric cytokines sharing the common p40 subunit, with receptors expressed on T, NK and NKT cells but low levels are present also on myeloid cells. Both cytokines are produced primarily by activated antigen presenting cells in response to toll like receptor stimulation (Gerosa et al. 2008; Trinchieri et al. 2003). For immune responses against most of bacterial pathogens, IL-12 is essential, while the IL-23 mediated induction of IL-17 might be essential for the rapid release of granulocytes in high pathogen infections (Christopher and Link 2007; Happel et al. 2005). In contrast, humans deficient for IL-12p40 or IL12Rb1 suffer exclusively from mycobacterial and salmonella infection but show normal resistance to most other pathogens, including viruses (Novelli and Casanova 2004).

IL-12 promotes IFN- γ -producing Th1 cells and the proliferation and cytotoxic activity of CD8+ T cells and NK cells. In preclinical tumor models, IL-12 induced IFN- γ promotes immune surveillance against transplanted syngeneic tumors. IFN- γ is not only rate limiting for T cell activity but also required for intratumoral expression of MHCI thereby increasing recognition of tumor antigens (Wong et al. 1984). Tumor immune surveillance in mouse models is largely dependent on IFN- γ expressing T cells (Kaplan et al. 1998). Experiments using IL-23 or IL-12 expressed in transplanted tumor cell or systemically were equally efficient in rejecting syngeneic transplanted tumors, however the mechanisms of IL-23 mediated anti-tumor activity are not clearly understood (Lo et al. 2003).

Cancer patients have been treated with recombinant IL-12 in several clinical studies, but dose limiting toxicities were observed before clinical benefits were achieved (Atkins et al. 1997). The toxicities were most likely manifestations of a systemic immune response brought about by high systemic IFN- γ expression. Subsequent attempts to combine IL-12 therapy with peptide vaccines have not yet revealed clearly enhanced clinical benefits (Cebon et al. 2003).

Despite the similarities between IL-12 and IL-23, IL-12 or IL-23 deficient animals have striking differences in tumor immune regulation. IL-12 deficiency in mice increases tumor incidence and allows for more rapid tumor growth. In contrast, deficiency in IL-23 or the IL-23 receptor dramatically reduces tumor incidence, and profoundly reduces established tumor growth (Langowski et al. 2006). IL-23 deficiency reduced anti-tumor immunosurveillance by locally increasing the presence of intratumoral CD8+ T cells. More importantly, the hallmarks of chronic inflammation such as metalloproteases, angiogenesis and macrophage infiltration were largely dependent on the presence and the amount of IL-23 in the host. The absence of IL-12 leads to exacerbation of the myeloid driven inflammation but with a coincident lack of CD8+ T cells (Langowski et al. 2006).

This proinflammatory function of IL-23 appears to orchestrate inflammatory tissue remodeling by the adaptive immune system. IL-23 controls IL-17 expression in T cells and other cell types. IL-17 can directly promote angiogenesis and matrix metalloproteinases (MMPs), two events that potentiate tumor growth

(Numasaki et al. 2003). In addition, IL-17 controls neutrophil chemotaxis, proliferation and maturation further fueling innate immune activation (Kolls and Linden 2004). Moreover, IL-17 producing CD8+ and CD4+ T cells have recently been reported to be widely present in human and mouse tumor microenvironments (Kryczek et al. 2007). The importance of IL-17 itself in the control of tumor growth however, is still debated and depends on the experimental setting (Kryczek et al. 2009b; Wang et al. 2009). In this context, it is noteworthy that IL-23 can induce, independent of IL-17, angiogenic erythema, inflammation and keratinocyte hyperproliferation and phenocopying aspects of human psoriatic lesions (Chan et al. 2006). Similarly, experimental encephalitis depends on IL-23 expression in the host (Cua et al. 2003) but IL17 or IL17F or both are dispensable (Haak et al. 2009).

In human cancers, IL-23p19 and IL12p40 are found to be over expressed in the majority of tumors, with IL-12p35 to be un-altered. IL-17 can be concomitantly upregulated in tumors or even lost in tumor progression (Kryczek et al. 2009a). It will be very important to understand the bifurcation of this pathway in cancer patients.

4 Feeding the Inflammatory Niche: Adaptive T Cell Responses Fostering the Tumor

How the adaptive immune system responds to perceived injury or infection is regulated on various levels, most intriguingly exemplified in the differential polarization of CD4+ helper cells (Reiner 2007 and Fig. 2). Cytokines such as IL-4, IL-12 and IL-23 regulate the initiation or activity of those divergent immunological pathways (McKenzie et al. 2006). IL-12 and IFN- γ prime and maintain the development of Th1 cells which produce IFN- γ and TNF- α and enhance antimicrobial and cytotoxic responses. IL-23 is essential in the proinflammatory function of a memory T cell subset characterized by the production of the cytokine IL-17, named therefore Th₁₇ (Aggarwal et al. 2003; Langrish et al. 2005). Through the attraction and activation of granulocytes and other innate myeloid cells, Th17 cells are thought to safeguard against extracellular bacteria. IL-17 engages its receptor, commonly found on stromal, epithelial, endothelial cells and monocytes – resulting in the release of additional inflammatory factors (such as IL-1, IL-6, IL-8, TNF- α , ProstaglandinE2, ICAM and several chemokines) to further the inflammatory cascade (Fossiez et al. 1998; Kolls and Linden 2004). Indeed, the IL-23/IL-17 inflammatory pathway, rather than the IL-12/IFN- γ pathway, has been highlighted by various recent reports as being central to inflammatory conditions exhibited in psoriasis, ischemic injury, inflammatory bowel disease (Yen et al. 2006), and autoimmune inflammation of the joint and brain (McKenzie et al. 2006). In those mouse models of inflammatory diseases Th₁₇ cells have been identified as the major pathogenic population (Langrish et al. 2005). Murine Th₁₇ cells develop from naïve

T cells under the influence of TGF- β and IL-6 (Mangan et al. 2006; Veldhoen et al. 2006). Th17 T cells express also IL-6, TNF- α and IL-22 a cytokine of the IL-10 family predominantly activating nonhematopoietic cell types. Recently, proinflammatory Th22 cells have been described from human blood, expressing a cytokine profile similar to Th17 but expressing different FGF isoforms instead of TNF- α (Eyerich et al. 2009). It is unclear if Th22 cells represent a separate helper cell lineage or a further polarization of the Th17 fate.

One important role for IL-23 was recently uncovered in its suppression of TGF- β mediated induction of the anti-inflammatory cytokine IL-10 (McGeachy et al. 2007). TGF- β stimulation increases the up-regulation of the Foxp3 transcription factor, inducing differentiation into regulatory T cells (Treg). Simultaneous stimulation with TGF- β and IL-6 diverted the CD4⁺ T cell toward the proinflammatory Th₁₇ cell (Bettelli et al. 2006). Since then numerous groups have confirmed the close relationship and the convertibility of regulatory T cells into proinflammatory Th17 cells (Yang et al. 2008).

The cytokines polarizing T cells towards Th17 or possibly Th22 such as IL-6, TGF- β , TNF- α , and IL-23 are also known to be present at high levels in the tumor environment and are typically associated with an unfavorable prognosis for human patient. IL-23 appears to be crucial for the function, survival and propagation of this important T cell population in the inflamed environment.

5 Turning Foes into Friends, CD8⁺ T Cells Lose Their Teeth

While most of the attention has been concentrated on IL-17 production by CD4⁺ T cells, there is more and more evidence that NK, $\gamma\delta$ T cells, and CD8⁺ T cells express IL-17 and are even in some instances the dominant source of this proinflammatory cytokine (He et al. 2006; Lockhart et al. 2006). Importantly, CD8⁺ T cells expressing IL-17 largely lack cytotoxic capacity (Liu et al. 2007).

CD8⁺ T cells deficient in the key transcription factors Eomes and Tbet fail to differentiate into functional cytotoxic T cells, do not control virus infection but induce multiorgan inflammation and death of the host in response to virus infection (Intlekofer et al. 2008). Those CD8⁺ T cells fail to express IFN- γ but up-regulate the transcription factor FOXp3, ROR γ T, the inflammatory cytokines IL-17 and IL-22 along with the IL-23 receptor. Most importantly, however, those Tc17 CD8⁺ T cells have a strongly reduced cytotoxic activity against antigen specific targets (Intlekofer et al. 2008). Recently, it has been shown that normal CD8⁺ T cells polarized in the combined presence of IL-6, TGF- β and IL-23 and the absence of IL-4 and IFN- γ differentiate into very similar Tc17 cells (Yen et al. 2009). Under those conditions CD8⁺ T cells gain the expression of Foxp3 and ROR γ t, IL-17 and IL-22, but have reduced levels of Eomes, Tbet and IFN- γ . Again, such polarized cells fail to produce cytotoxic enzymes and also fail to kill cognate target cells. However, when transferred into mice Tc17 cells reverted rapidly into IFN- γ and TNF- α expressing Tc1 cells demonstrating that the phenotypic plasticity might be

determined by the local cytokine milieu. Unexpectedly, extraction of IFN- γ producing Tc1 like CD8+ T cells was more efficient when Tc17 were transferred, than after transfer of bona fide Tc1 cells, indicating that the IL-17 producing population displayed a marked increase in the capability of *in vivo* expansion (Yen et al. 2009). Interestingly, CD8+ T cells with a very similar differentiation pattern have been described to promote tumor progression in carcinogen induced skin tumors in mice (Kwong et al. 2009). Here, tumor infiltrating CD8+ T cells fail to express cytotoxic characteristics but express all the hallmarks of an inflammatory T cell *in vivo*, such as IL-17 and IL-22. Importantly, deficiency of CD8+ T cells in this model of skin carcinogenesis lead not to increased tumor formation but to a decreased progression rate from benign tumors to carcinomas (Roberts et al. 2007).

Taken together, the recent data suggest that both CD4+ and CD8+ T cells can not only fail to support the elimination of malignant cells but they may significantly contribute to tumor progression. Such noncytotoxic cells may possibly drive the physiological changes seen in late stage cancer patients, such as inflammatory multi organ failure.

6 Inflammatory Control at the Tumor Site

There is considerable controversy concerning the volatility of the polarization of an adaptive immune response. As it pertains to the regulation of tumor immunity, one has to note that immunization protocols and adaptive T cell transfers typically result in Th1 or Tc1 polarized T cell responses. Despite strong antigen specific *in vitro* activities of such induced or transferred cells, their therapeutic effectiveness does not, in most cases satisfy expectations. In the tumor microenvironment, the same T cells appear to lose their function or fail to infiltrate the tumor altogether. An attractive explanation for this phenomenon is the induction of energy or functional depolarization in the local environment.

In inflammatory models, where Th17 polarized cells are pathogenic through the activation and attraction of myeloid cells and neutrophils, it had been shown that the pathogenic effect of the transferred IL-17 producing T cells was stable and still dependent upon IL-17 *in vivo* (Langrish et al. 2005). Th17 cells can however swiftly repolarize into Th1 cells when transferred in the appropriate host (Bending et al. 2009).

Adoptive transfer of tumor specific Th17 into mice harboring primary irradiated tumors or experimental lung nodules of B16 melanoma cells reduced their tumor burden. The anti-tumor effects appeared to depend on the presence of host IFN- γ R, but antibody mediated depletion of IFN- γ did not change the outcome (Martin-Orozco et al. 2009; Muranski et al. 2008). It is therefore not clear if in the anti-tumor function of proinflammatory Th17 induced anti-tumor effects by attracting myeloid cells, or if the transferred cells reverted to a Th1 profile *in vivo*.

CD8+ T cells polarized and sorted for the IL-17+ population revert very efficiently in lung tissue expressing the cognate antigen from IL-17 to IFN- γ production

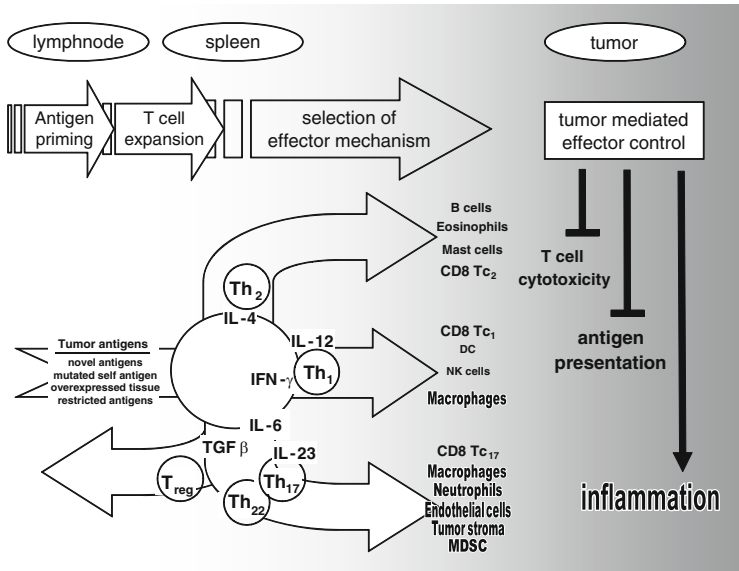


Fig. 3 *Location – Location – Location*. Cancer patients can have systemic tumor specific responses, but the frequency of cytotoxic memory T cells in the tumor tissue is typically low and their presence correlates positively with clinical outcome. While priming and expansion of tumor antigen specific T cells in secondary lymphoid organs might not be abrogated, the resulting immune response is blunted and altered in the local, immune deviating microenvironment of the tumor

(Yen et al. 2009). Importantly, Foxp3+ regulatory T cells express inflammatory Th17 polarization when isolated from intestinal polyps of APC-Min mice (Gounaris et al. 2009). Similarly, the transition from a Treg to a Th17 cell has been observed by several groups and is influenced by IL-6 or IL-1 and stabilized by IL-23, the same cytokines influencing the differentiation of naïve cells (Yang et al. 2008 and Fig. 3).

Inflammatory cytokines like IFN- γ and IL-12 or TGF- β , IL-6 and IL-23 appear to control the bifurcation of tumor infiltrating immune cells into tumor immune surveillance or tumor associated inflammation respectively. In the local tumor microenvironment, IL-23 induces the hallmarks of chronic inflammation such as metalloproteases, angiogenesis and macrophage infiltration, but it also reduces anti-tumor immunosurveillance by locally suppressing the presence of CD8+ T cells. The absence of IL-12 lead to an exacerbation of the myeloid driven inflammation with a coincident lack of CD8+ T cells (Langowski et al. 2006). Increased CD8+ T cell infiltration and enhanced tumor immune surveillance was observed when IL-12 dominated IL-23, either in the absence of IL-23 or upon injection of IL-12. IL-12 and IL-23 induce differential chemokine patterns (MO unpublished), but it is not clear if differential chemoattraction causes the local immune polarization. Also, it remains to be shown if other tumor associated proinflammatory cytokines reduce the local CD8+ T cell response in similar ways.

Moreover, IL-12 and IL-23 can regulate inflammation independently of T cells. Rag deficient mice treated with an activating anti-CD40 antibody developed an IL-23

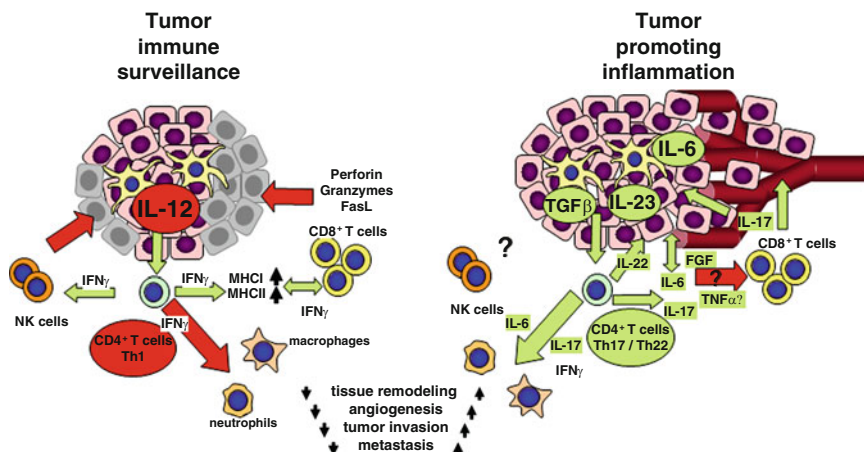


Fig. 4 *IL-23 mediated deviation from a cytotoxic immune response.* Exposure to novel antigens in an inflammatory milieu stimulates antigen specific immune responses. However the composition of the local cytokine milieu regulates which effector molecules and cells are deemed appropriate to eliminate the challenge. The activation of inappropriate cytokine cascades, might not only inhibit efficient elimination of tumor cells but might also contribute to immune pathologies, promoting tumor growth by providing an essential growth environment. *Green arrow:* stimulation, *red arrow:* inhibition. *Green highlight:* tumor promoting or tumor associated mechanism

dependent colitis while the wasting syndrome observed in wt mice was dependent on the systemic function of IL-12 (Uhlig et al. 2006). This observation might have some importance for human cancer patients where systemic inflammatory responses including elevated levels of IFN- γ in the serum are thought to underlie weight loss in cancer associated cachexia.

In preclinical tumor models, IL-12 and IFN- γ promote immune surveillance against endogenous and transplanted syngeneic tumors (Koebel et al. 2007). IFN- γ is not only rate limiting for T cell activity but required for the expression of intratumoral MHCI thereby enabling the recognition of tumor antigens (Wong et al. 1984). In many human tumors, MHCI is expressed only at very low levels, unless induced by IFN- γ (Seliger et al. 2002). In the absence of IL-12, or in a local cytokine milieu preventing Th1 differentiation and IFN- γ expression, MHCI expression might be limited and the recognition of the tumor specific epitopes by CD8⁺ T cells might be far less efficient (Fig. 4).

7 Conclusions

For centuries, increased cancer incidence has been observed in locations of chronically inflamed, damaged tissue, and there exists a correlation between high serum concentrations of immune stimulating inflammatory cytokines and detrimental prognosis for human cancer patients.

Only recently have we begun to understand the molecular mechanisms of how and why tumors occur more frequently in an inflammatory microenvironment and why tumors seem to perpetuate such conditions throughout their progression. Not surprisingly proinflammatory cytokines are at the crossroad of this altered regulation. As described above several of these cytokines are highly expressed in human cancers (Figs. 2 and 4) and alter the adaptive immune response in several ways that are simultaneously beneficial to tumor growth. Antigen specific cytotoxicity, in particular by CD8+ T cells, is blunted while the inflammatory responses to the same tumor antigen are unaltered and even enhanced. Several of the cytokines involved in the inflammatory regulation are either fueled by Th17 or possibly Tc17 T cells or foster their development. Therapeutic expansion of the tumor antigen specific immune response might therefore fail to eliminate the tumor but stimulate tumor specific but noncytotoxic inflammation.

It is tempting to speculate that the observed derailing of anti-tumor immunity into an inflammatory response is at its core a defensive strategy of the tumor, selected for independently of the tumor cell transformation. Expression of the inflammatory cytokines such as IL-23 by the tumor cell can be seen as evidence for this model. At first the presence of mutant cell clones in an inflamed and regenerating tissue could simply be an unfortunate coincidence. Tumor cells fostering this cytokine milieu may be preferentially selected due to improved cytokine mediated growth conditions for the nascent tumor while the same cytokines such as IL-23 may inhibit the immune mediated tumor surveillance elimination.

Alternatively, inflammation induction might be the mere result of, and the default reaction to the expression of transforming oncogenes within the tumor cell. The observation that necrosis, often seen as a consequence of oncogene activation or chemo-therapeutic intervention, fosters inflammation provide support for the latter explanation (Fonseca and Dranoff 2008).

It remains to be seen if selective therapeutic blockade of inflammation can deliver benefits to patients suffering from large tumors, rather than merely serving a prophylactic role potentially preventing cancer occurrence and inhibiting early cancer growth. The simultaneous inhibition of inflammation and the induction of cytotoxicity may be necessary to eliminate tumor cells in the tumor and in micro-metastatic sites.

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