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Up for Mischief? IL-17/Th17 in the tumour microenviroment

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Abstract

The role of IL-17 and the IL-17 producing Th17 cells in cancer has recently become the focus of extensive investigation. An expanding body of literature implicate Th17 cells and their hallmark cytokine in both pro and anti-tumourigenic processes. In this review we describe their biological activities and outline the reciprocal interactions between Th17 cells and other cells of the immune system. We also discuss the evidence regarding their dual role in the tumour microenvironment. An understanding of the processes that regulate the pro or anti-tumour activities of Th17 cell and IL-17 will allow the development of more effective means for cancer immunotherapy.

Keywords

IL-17; Th17; cancer; inflammation; tumour microenvironment

Introduction

Cancer cells are characterized by a great potential to proliferate and evade apoptosis as well as a capacity to develop blood vessels, invade tissues and metastasize (Hanahan and Weinberg, 2000). These complex processes reflect intrinsic properties of the malignant cells but are also markedly regulated by non-neoplastic components in the tumour microenvironment (Colotta *et al.*, 2009). Innate and adaptive immune cells including macrophages, neutrophils, mast cells and lymphocytes are present in most solid tumours. These cells mediate inflammatory responses that are necessary for both tumour progression and the elimination of malignant cells (Coussens and Werb, 2002; Dunn *et al.*, 2004). For instance $CD8^+$ cytotoxic T lymphocytes, interferon-γ (IFN-γ)-producing T helper 1 (Th1) cells, dendritic cells (DCs) and 'M1' macrophages secreting interleukin-12 (IL-12) mediate anti-tumour immunity (Dunn *et al.*, 2004; Boon *et al.*, 2006). In contrast, M2 macrophages, type 2 helper T cells and regulatory T cells (Tregs) have been found to enhance tumour development (Beyer and Schultze, 2006; Roberts *et al.*, 2007; Sica and Bronte, 2007; DeNardo *et al.*, 2009). Moreover, it has become evident that tumour cells are able to breach the host's immune defences and divert the immune response in order to achieve progressive growth (Dunn *et al.*, 2004). The driving initiator is still an oncogenic mutation leading to

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autonomous cell growth; however several genetic mutations have been demonstrated leading to the expression of chemokines and cytokines by the malignant cells (Mantovani *et al.*, 2008). The result is a picture similar to inflammation with contribution of this inflammatory milieu to cancer progression.

IL-17, a widely recognised inflammatory cytokine, and the IL-17 producing Th17 cells have recently gained prominence in cancer. Despite the rapid advances in understanding their role in inflammation and autoimmunity, their activity in cancer yields conflicting data. In this review we will focus on the biological functions of IL-17 and discuss the settings in which IL-17 and Th17 cells have been found to exert a pro- or anti-tumourigenic effect.

IL-17 expression, receptor signalling and biological activities

IL-17 (also called IL-17A) is the prototypic member of the IL-17 family composed of six cytokines, IL-17A-F (Aggarwal and Gurney, 2002; Gaffen, 2004; Huang *et al.*, 2004; Kolls and Linden, 2004). IL-17 is the hallmark cytokine of Th17 cells and along with IL-17F, with which shares the greatest homology, is also produced by γδT cells, natural killer (NK) T cells, neutrophils and eosinophils (Molet *et al.*, 2001; Starnes *et al.*, 2001; Ferretti *et al.*, 2003; Zhou *et al.*, 2005; Lockhart *et al.*, 2006; Liu *et al.*, 2007). IL-17A/F signals through IL-17RA, a type I transmembrane protein ubiquitously expressed (Moseley *et al.*, 2003; Yang *et al.*, 2008a). IL-17RA activates mitogen activated protein kinases (MAPK) and nuclear factor-kB (NF-κB) via TNF receptor associated factor-6 (TRAF6) and has also been found to physically associate with the NF-κB activatory protein (Act1) (Shalom-Barak *et al.*, 1998; Schwandner *et al.*, 2000). Knock down of Act1 was subsequently shown to abrogate IL-17 induced inflammatory gene expression as well as NF-κB activation (Chang *et al.*, 2006).

In vivo

A large body of evidence suggests that IL-17A and IL-17F mediate local tissue inflammation by inducing the release of pro-inflammatory and neutrophil mobilising cytokines and chemokines. *In vivo* administration of recombinant IL-17A causes significant accumulation of neutrophils in the bronchioalveolar and joint areas (Hoshino *et al.*, 1999; Laan *et al.*, 1999; Hoshino *et al.*, 2000; Miyamoto *et al.*, 2003) and leads to disease progression in a syngeneic model of ovarian cancer (Charles *et al.*, 2009). CXC-chemokine ligand-1 (CXCL1), CXCL2, IL-6 and granulocyte monocyte-colony stimulating factor (GM-CSF) have been found to mediate the neutrophil recruitment caused by IL-17A in similar *in vivo* experimental systems (Hoshino *et al.*, 1999; Laan *et al.*, 1999; Ferretti *et al.*, 2003; Kolls *et al.*, 2003; Laan *et al.*, 2003). IL-17A has also been found to increase neutrophil elastase and myeloperoxidase (MPO) activity *in vivo* (Hoshino *et al.*, 2000). Interestingly, it has been observed that upon local administration, IL-1β and IL-17A can synergistically increase neutrophil activity but not neutrophil accumulation suggesting a negative regulatory role for IL-17A in the presence of an inflammatory stimulus promoting the late phase and resolution of inflammation (Hoshino *et al.*, 2000). By regulating neutrophil response IL-17A is also a crucial element in host responses to infections. For instance, in response to infections of gram-negative bacteria such as *Klebsiella pneumoniae* IL-17A is induced in a dose dependent manner and is critical for neutrophil recruitment (Ye *et al.*, 2001a; Ye *et al.*, 2001b).

In vitro

In vitro experiments have shown that IL-17A and F stimulate the production of several CXC chemokines, CXCL1, CXCL2 and CXCL5 in mouse fibroblasts and epithelial cells (Fossiez *et al.*, 1996; Laan *et al.*, 1999; Kawaguchi *et al.*, 2001; Laan *et al.*, 2001; Jones and Chan,

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2002; Prause *et al.*, 2004). They also induce CXCL1, CXCL2, CXCL5 and IL-8 (also known as CXCL8) in human epithelial cells. IL-17A induced release of CXC chemokines has been shown to involve MAPK and the extracellular signal-regulated kinase (ERK) (Kawaguchi *et al.*, 2001; Laan *et al.*, 2001; Prause *et al.*, 2004). In addition to CXC chemokines IL-17A can induce the release of granulocyte-colony stimulating factor (G-CSF) and GM-CSF (Jones and Chan, 2002; Starnes *et al.*, 2002) as well as the monocyte chemotactic protein (MCP)-1 and IL-6 in epithelial cells and fibroblasts (Yao *et al.*, 1995; Kawaguchi *et al.*, 2001; Molet *et al.*, 2001). More interestingly, in response to IL-17A monocytes isolated from human peripheral blood release tumour necrosis factor-α (TNF-α) and IL-1β (Jovanovic *et al.*, 1998). In contrast, alveolar and peritoneal macrophages fail to produce TNF-α, CXCL2 or IL-6 in response to IL-17A (Kolls *et al.*, 2003).

Responses to IL-17A can functionally cooperate with responses to other inflammatory cytokines and maximise their biological effects or, as indicated above, in case of e.g. IL-1β modulate inflammatory responses. For example, IL-17A markedly synergises with TNF-α in inducing G-CSF, CXCL1 and IL-8 production by epithelium (Jones and Chan, 2002; McAllister *et al.*, 2005). Costimulation with IL-17A and IFN-γ enhances the IL-8 response in human bronchiolar epithelial cells and increases intercellular adhesion molecule-1 (ICAM-1) (Kawaguchi *et al.*, 2001). In contrast, the Th2 cytokines IL-4 and IL-13 have no additional effect on ICAM expression (Kawaguchi *et al.*, 2001). Overall, the response to IL-17 seems to be context dependent. The majority of research work currently focuses on the biological role of IL-17A and distinctions between the six IL-17 family members in their biological activity are missing. Further studies on the regulation and biological function of these cytokines will benefit our understanding of immune responses.

IL-17 in malignancy

IL-17 has been well studied over recent years in inflammatory diseases, but what about its role in tumour development and malignant progression? IL-17A expression has been detected in several human tumours including prostate, breast and gastric cancer (Haudenschild *et al.*, 2002; Steiner *et al.*, 2003; Sfanos *et al.*, 2008; Zhang *et al.*, 2008; Derhovanessian *et al.*, 2009; Horlock *et al.*, 2009). However, the specific role of IL-17 in cancer is still elusive. IL-17A ectopically overexpressed in murine fibrosarcoma or colon adenocarcinoma cell lines can significantly enhance *in vivo* tumour growth and increase tumour vascularity (Numasaki *et al.*, 2003), (Table 1). It can also stimulate endothelial cell cord formation and up-regulate the production of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), prostaglandin E1 (PGE1) and PGE2 (Numasaki *et al.*, 2003). Notably, both cell lines used in those studies are weakly immunogenic. In line with these findings, human cervical cancer cell lines stimulated with recombinant IL-17 up-regulate IL-6 and IL-8 and when transfected with IL-17 cDNA they show significantly higher tumour growth in athymic nude mice (Tartour *et al.*, 1999). However, when immunogenic hematopoietic tumour cells overexpressing IL-17 are implanted into syngeneic immunocompetent mice tumour growth is significantly inhibited (Benchetrit *et al.*, 2002). Although the basis of these differences is not well understood, it appears that IL-17 enhances anti-tumour immunity in immunocompetent mice but can increase tumour growth in the absence of an adaptive immune response (Martin-Orozco and Dong, 2009).

More recent studies evaluated the role of endogenous IL-17 in tumour immunopathogenesis. Wang *et al.* showed that growth of the B16 melanoma and the MB49 bladder carcinoma cells is reduced in IL-17$^{-/-}$ mice but accelerated in IFN-γ$^{-/-}$ mice due to elevated intratumoural IL-17 (Wang *et al.*, 2009), (Table 1). Interestingly, IL-17/IFN-γ double knockout mice are resistant to tumour cell growth similarly to the IL-17$^{-/-}$ suggesting a minor role of IFN-γ in IL-17 mediated tumour promotion. IL-17 stimulated IL-6 production

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via signal transducer and activator of transcription 3 (Stat3) activation in B16 and MB49 tumour cells, as well as in tumour associated stromal cells such as fibroblasts, endothelial cells and dendritic cells. However, it only modestly increased tumour cell proliferation *in vitro*. IL-17 also increased the secretion of angiogenic factors by endothelial cells and induced endothelial cell migration in a Stat3-dependent manner. Tumours grown in IFN-$\gamma^{-/-}$ mice were characterised by markedly elevated levels of IL-17 and IL-6 produced mainly by tumour infiltrating immune cells but also by tumour cells. *In vivo* IL-6 blockade partially reversed tumour progression in this setting indicating that the tumourigenic effects of IL-17 are mediated in part via IL-6, in a Stat3-dependent pathway (Wang *et al.*, 2009).

Similarly, tumour growth is inhibited in IL-17R$^{-/-}$ as well as IL-17R/IFNγR$^{-/-}$ mice (He *et al.*, 2010). The IL-17R deficiency increased tumour-specific CD8$^+$ T cell infiltration while it reduced recruitment of immature myeloid cells. Further analysis of the tumour infiltrating CD8$^+$ T cells showed that IL17R deficiency did not impair their cytotoxic acivity or the expression of cytotoxic T lymphocyte (CTL)-related molecules such as perforin, granzyme B and FasL.

Kryczek and colleagues, however, demonstrated a protective role of IL-17 in tumour immunity (Kryczek *et al.*, 2009b). They showed, accelerated growth and enhanced lung metastasis of the murine colon cancer cell line MC38 when inoculated in IL-17$^{-/-}$ mice (Table 1). The underlying mechanism for the increased tumour growth in IL-17 deficient mice was considered to be a reduction in IFN-γ producing NK cells and CD8$^+$ T cells. Notably, Ngiow *et al.* failed to reproduce the MC38 enhanced growth in IL-17$^{-/-}$ mice and indicated that although T and NK cells were exerting some host control on tumour development, this was not dependent on IL-17 production {Ngiow, 2010 #128}. Nevertheless, accelerated tumour growth was also observed in IL-17$^{-/-}$ mice challenged with the B16-F10 melanoma cell line that colonizes the lung (Martin-Orozco *et al.*, 2009b). The discrepancy between these studies and the report by Wang *et al.* is possibly due to distinct roles of IL-17 in different tumour models mirroring the tissue and context dependency described in inflammatory models.

The majority of the studies investigating the role of IL-17 in tumour development have been conducted on implanted tumour models. The limitation of such models is that they may only show the effects of IL-17 on established tumours that do not grow at their original anatomical sites. The study of IL-17 in genetic, chemical or microbial induced tumour models is limited and mainly studied in relation to Th17 immune responses as will be discussed below. Certainly, further investigations are required to determine the basis of these differences and to clarify the role of IL-17 in the tumour microenvironment.

Tumour infiltrating Th17 cells

IL-17 is the signature cytokine of Th17 cells. An expanding body of studies indicates that Th17 cells are present at tumour sites (Table 1). These cells appear to constitute a minor population in human peripheral blood and lymph nodes with no major frequency changes in cancer patients compared to healthy donors (Kryczek *et al.*, 2009a). There is however a strikingly high frequency of tumour infiltrating IL-17$^+$ T cells in patients with diverse cancer types, including ovarian and pancreatic cancer (Kryczek *et al.*, 2007; Kryczek *et al.*, 2009a; Su *et al.*, 2010). Similar to human, Th17 cells are found to infiltrate tumours in murine models of cancer while being minimal in peripheral tissues of normal mice (Kryczek *et al.*, 2007). Moreover, the levels of intratumoural Th17 cells are increased in advanced tumour stages but remain minimal in the draining lymph nodes (Kryczek *et al.*, 2007). The presence of Th17 cells in the tumour microenvironment raises the question about their recruitment, *in situ* differentiation and, most importantly, their role in tumour immunity.

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Phenotypic and tissue-homing features

Tumour-infiltrating Th17 cells exhibit a memory phenotype ($CD45RA^{-}CD45RO^{+}$) and a range of receptors that allow them to traffic in the periphery. They have been found to express high levels of CXCR4 and CCR6 as well as the tissue homing C type lectin CD161, a molecule found on NK cells and $CD8^{+}$ T cells (Kryczek *et al.*, 2008; Muranski *et al.*, 2008; Kryczek *et al.*, 2009a; Martin-Orozco and Dong, 2009). They also express the gut homing CD49 integrins but not CCR2, CCR5 and CCR7 and therefore have a limited capacity of lymph node trafficking (Kryczek *et al.*, 2009a). This pattern of receptors may be associated with a selective Th17 cell migration and retention within tumour sites as high levels of CCL20 and CXCL12 are present in the tumour microenvironment (Zou *et al.*, 2001; Kryczek *et al.*, 2005; Rubie *et al.*, 2006; Aspord *et al.*, 2007; Ghadjar *et al.*, 2009). Nevertheless Th17 cells have also been found to produce CCL20 and can therefore promote their own frequency at the tumour site (Muranski *et al.*, 2008).

Kryczek *et al.* further analysed the phenotype of tumour infiltrating Th17 and reported low levels of the activation markers HLA-DR and CD25 as well as low levels of granzyme B suggesting that they may not be conventional effector T cells and may not mediate cytotoxic killing via the granzyme B pathway (Kryczek *et al.*, 2009a). On the other hand reduced levels of forkhead box P3 (Fox3) and the B7-H1 receptor, programmed cell death-1 (PD-1), both of which contribute to immunosuppression in the tumour microenvironment (Kryczek *et al.*, 2009a).

Th17 regulation in the tumour microenvironment

Cytokine networks

Malignant cells and associated stromal cells, such as fibroblasts and antigen presenting cells (APCs), secrete large amounts of IL-1β, IL-6, IL-23, TNF-α and transforming growth factor-β (TGF-β); key cytokines in Th17 differentiation and expansion (Hodge *et al.*, 2005; Balkwill, 2006; Langowski *et al.*, 2006; Miyahara *et al.*, 2008; Su *et al.*, 2010). Upon exposure to TGF-β in combination with IL-6 or IL-21 naïve T cells initiate the Th17 differentiation programme characterized by expression of IL-17 and IL-21 and the transcription factor retinoic acid-related orphan receptor-γt (RORγt) (Bettelli *et al.*, 2006; Mangan *et al.*, 2006; Veldhoen *et al.*, 2006), (Figure 1). IL-23 subsequently stabilises the Th17 phenotype. As far as human Th17 are concerned, the combination of TGF-β, IL-1β plus IL-6, IL-21 or IL-23 is essential for their polarisation from naïve cells whilst TGF-β plus IL-6 is sufficient to drive IL-17 production in murine T cells (Bettelli *et al.*, 2006; Mangan *et al.*, 2006; Veldhoen *et al.*, 2006; Manel *et al.*, 2008; Volpe *et al.*, 2008). A number of studies originally claimed that TGF-β may be dispensable in humans (Acosta-Rodriguez *et al.*, 2007; Wilson *et al.*, 2007). The experimental protocols used to isolate naïve T cells and a TGF-β contamination in the culture system are believed to account for this discrepancy (Manel *et al.*, 2008; Volpe *et al.*, 2008; Yang *et al.*, 2008b).

TGF-β has a dual function in T cell polarisation by directing the differentiation of both Th17 cells and Tregs pending the polarising cytokines. Stimulation of naïve T cell with TGF-β alone induces expression of both Foxp3 – the transcription factor that guides Treg differentiation– and RORγt (Ivanov *et al.*, 2006; Zhou *et al.*, 2007). In TGF-β-induced naïve T cells, despite the presence of RORγt, the Foxp3-directed programme of Treg cell differentiation prevails. This is, at least in part, due to Foxp3 counteracting RORγt function (Zhou *et al.*, 2008). However, in the presence of IL-6, IL-21 or IL-23, Foxp3 activity is inhibited while RORγt is upregulated and stabilised allowing the progression towards the IL-17 lineage (Zhou *et al.*, 2008). The signalling pathways initiated after binding of both IL-6 and IL-21 to their receptors in naive $CD4^{+}$ T cells are dependent on Stat3 (Zhou *et al.*,

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2007). Stat3 cooperates with RORγt to induce maximum IL-17 expression and optimal Th17 polarization. In addition to IL-17, it induces the transcription of IL-23 and IL-23R on naive T cells and stabilises the Th17 phenotype (Zhou *et al.*, 2007).

TNF-α, present within the tumour microenvironment, has also been implicated in Th17 polarization. Although TNF-α is not essential for Th17 differentiation from naïve T cells, it synergises with IL-6 and IL-1β to amplify Th17 responses (Veldhoen *et al.*, 2006). Furthermore, recent studies by our group indicate that TNF-α enhances Th17 differentiation by increasing IL-1R and IL-23R expression (Charles *et al.*, 2009). More interestingly, microarray data generated from human ovarian cancer revealed significant association between high TNF-α signalling pathway gene expression and expression of genes of the Th17 pathways.

Interaction with the tumour microenvironment

Coculture of naïve and memory $CD4^+$ T cells with tumour cells plus APCs can generate high percentages of Th17 cells (Miyahara *et al.*, 2008). IL-1β appears to be critical in this setting while IL-6 and IL-23 is important only for the expansion of memory Th17 cells (Miyahara *et al.*, 2008). Further studies dissect the contribution of tumour associated macrophages (TAMs) and DCs in Th17 polarization (Kryczek *et al.*, 2009a). TAMs and myeloid DCs isolated from human ovarian cancers can polarize memory but not naïve T cells towards a Th17 phenotype. TAMs express higher levels of IL-1β and IL23p19 and are more efficient in inducing Th17 cells compared to normal macrophages (Kryczek *et al.*, 2009a). Blocking IL-1β, but not IL-6 or TGF-β, reduced TAM mediated Th17 induction. Plasmacytoid DCs have minimal effect on Th17 polarization and as TAMs outnumber DCs in cancers they may be the predominant Th17 inducers in the tumour microenvironment (Kryczek *et al.*, 2009a).

Tumour cells, fibroblasts and endothelial cells release several cytokines and C-C ckemokines such as MCP-1, MIP-1α and CSF-1 which contribute as major chemoattractants involved in monocyte/macrophage recruitment into the tumour (Coussens and Werb, 2002; Murdoch *et al.*, 2004; Siveen and Kuttan, 2009). Th17 cells can in turn favour the recruitment of APCs by releasing CCL20 or inducing the release of this chemokine by resident cells (Martin-Orozco *et al.*, 2009b). CCL20 leads to chemotactic recruitment of DCs via CCR6 which might in turn create a positive feedback loop between recruited DCs and Th17 cells promoting their frequency at the tumour site.

Tregs are found at high frequencies in the tumour microenvironment and have been shown to have a critical role in hampering anti-tumour immunity (Zou, 2006). More interestingly, the Th17 and Treg differentiation programmes are reciprocally related. This suggests a dynamic interaction between Treg and Th17 cells in the tumour microenvironment. Indeed, several studies have shown that naïve ($CD45RO^-$) and memory ($CD45RO^+$) Tregs can be induced to secrete IL-17 in the presence of IL-2, IL-1β, IL-6, IL-21, or IL-23. (maha ayyoub 26 106), (valmori 131 298) (Xu *et al.*, 2007; Yang *et al.*, 2008b; Voo *et al.*, 2009). IL-2 alone has been shown to mediate the coversion of ovarian cancer-associed Tregs into IL-17 producers. (Leveque 32 101) . Notably, systemic administration of IL-2 in tumour bearing mice results in increased numbers of $Foxp3^+$ T regs in the tumour and draining lymph nodes whilst tumour-associated $IL\text{-}17^+$ cells are significantly reduced. Furthermore IL-2 appears to inhibit the differentiation of Th17 cells from mouse splenocytes in a Stat5-dependent manner but enhance development of Tregs (Laurence 26 371) (Kryczek *et al.*, 2007). It is, therefore, possible that IL-2 has an opposite effect on differentiation of Th17 cells from conventional $CD4^+$ T cells and Tregs (Leveque 32 101).

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In line with the notion of a Treg-Th17 transition at tumour sites, a subpopulation of $CD4^+Foxp3^+IL\text{-}17^+$ cells can be detected in humans (Leveque 32 101) (Voo *et al.*, 2009). These cells co-express CD25, Foxp3, IL-17 and RORγt and maintain a suppressive function via a cell-cell contact mechanism (Voo *et al.*, 2009). Whether these coexpressors derive from Treg or Th17 cells has not been demonstrated but they appear to represent a transition stage between Treg and Th17 cells. The plasticity of Tregs and the cytokine milieu at tumour sites may therefore allow an initial shift towards the IL-17 producing subpopulation and subsequently the development of Th17 cells.

Despite the high levels of IL-6, IL-1β and TGF-β in the tumour microenvironment, Th17 cells are present at lower frequencies compared to Tregs. High amounts of TGF-β can inhibit Th-17 differentiation even in the presence of pro-inflammatory cytokines (Manel *et al.*, 2008). The relative amounts of these cytokines may therefore determine the Th17 or Treg lineage choice. Alternatively, other factors present at the tumour site may counteract the positive effect of pro-inflammatory cytokines on Th17 development. For instance, IL-2 inhibits Th17 differentiation while enhancing the Treg subset both *in vitro* and *in vivo* (Kryczek *et al.*, 2007). Furthermore, retinoic acid, a vitamin A metabolite, inhibits the IL-6 mediated induction of IL-17 from $Foxp3^+$ cells (Yang *et al.*, 2008b). Whether retinoic acid plays a role in the Treg-Th17 balance in the tumour microenvironment is currently not known. Murine Tregs also directly repress Th17 responses *in vivo* in a Stat3 dependent manner. Ablation of Stat3 in Tregs leads to loss of their suppressive functions and their ability to control Th17 cells (Chaudhry *et al.*, 2009).

The pro and anti-tumour activity of Th17 cells

Pro-tumour

Inflammatory can promote malignant cell transformation, tumour growth and metastasis (Mantovani *et al.*, 2008). Th17 cells are characterised by potent pro-inflammatory activities mediated predominantly by their effector cytokines IL-17A and F, IL-21, IL-22 and IL-23. The major pro-tumour roles of Th17 cells rely on their capacity to induce angiogenesis, recruit inflammatory cells and activate tumour-promoting transcription factors (Figure 2). As already mentioned, by acting on stromal cells and fibroblasts IL-17 induces a wide range of angiogenic factors such as VEGF. Not surprisingly, the levels of IL-17 producing $CD4^+$ T cells have been positively correlated with microvessel density in tumours (Numasaki *et al.*, 2003). Interestingly, VEGF induces TGF-β while TGF-β can in turn upregulate expression of VEGFR receptor on endothelial cells thereby enhancing their responsiveness to VEGF (Huang and Lee, 2003).

Human Th17 cells can directly attract neutrophils through the production and release of IL-8 (Pelletier *et al.*). This may represent a more efficient mechanism for Th17 cells to rapidly recruit and interact with neutrophils as opposed to the indirect actions of IL-17A/F which mediate their effect via induction of chemokine secretion by epithelial and endothelial cells (Jones and Chan, 2002). The same study also shows that Th17 cells are able to modulate neutrophil responses via the release of GM-CSF, TNF-α and IFN-γ in an IL-17 independent manner. This Th17-neutrophil interaction appears to be bidirectional as activated neutrophils can also recruit Th17 in a CCL20/CCR6 dependent manner (Pelletier *et al.*, 2010). Interestingly, tumour infiltrating neutrophils are associated with poor prognosis and their capacity to modify tumour growth and invasiveness led to suggestion of a N1/N2 phenotype differentiation similar to the M1/M2 polarisation (Haqqani *et al.*, 2000; Sparmann and Bar-Sagi, 2004; Nozawa *et al.*, 2006; Fridlender *et al.*, 2009). A recent study demonstrates that neutrophil elastase is secreted upon neutrophil activation and can directly induce tumour cell proliferation both in human and mice. Moreover, in a murine model of lung

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adenocarcinoma, mice lacking neutrophil elastase have markedly decreased tumour burden (Houghton *et al.*, 2010).

Stat3 has a central role in tumour immunity by promoting pro-oncogenic inflammatory pathways such as NF-κB and Jak pathways and by counteracting Stat1 and NF-κB mediated anti-tumour Th1 responses (Yu *et al.*, 2009). Th17 derived IL-17, induces IL-6 production by malignant as well as tumour stromal cells which in turn activates Stat3 in both tumour and stromal cells in the tumour microenvironment (Wang *et al.*, 2009). Beyond its role on malignant cells and the tumour stroma Stat3 is a critical transcription factor for Th17 differentiation. Its activation in the tumour microenvironment inhibits IL-12p35 while enhancing IL-23p19 transcription thereby shifting the balance from IL-12 to IL-23 (Langowski *et al.*, 2006; Kortylewski *et al.*, 2009). Given the close relation of IL-23 with Th17 cell development and along with the finding that chemical-induced skin carcinogenesis is diminished in IL-23p19$^{-/-}$ mice and enhanced in IL-12p35$^{-/-}$ mice it is suggested that Stat3 promotes a pro-carcinogenic Th17 response (Kortylewski *et al.*, 2009). More recently, the notion of a crucial pro-tumorigenic effect of Th17 cells driven by Stat3 activation is further confirmed in infection induced colon carcinogenesis (Wu *et al.*, 2009).

Anti-tumour

Although tumour infiltrating Th17 cells appear to have pro-tumour activity another line of evidence suggests that they may mediate protective anti-tumour immunity (Figure 2). Muranski and colleagues used T cell receptor (TCR) transgenic mice specific for a melanoma epitope and polarised CD4$^+$ T cells towards Th17 in the presence of IL-6 and TGF-β. Upon adoptive transfer into mice with established cutaneous melanoma, these cells mediated effective tumour rejection, better than Th1 polarised cells (Muranski *et al.*, 2008). Interestingly, their effect was critically dependent on IFN-γ whereas depletion of IL-17A and IL-23 had little impact (Muranski *et al.*, 2008). In a similar study, CD8$^+$ T cells were skewed to secrete IL-17 in Th17 polarising conditions and mediated efficient tumour destruction when adoptively transferred into tumour bearing mice. Again, the response was highly dependent on IFN-γ as these cells were found to convert into IFN-γ producers (Hinrichs *et al.*, 2009). IL-17 derived from Th17 cells and IFN-γ can synergistically induce the secretion of the Th1 type CXCL9 and CXCL10 by tumour cells which in turn potentially attract effector T cells at the tumour site (Kryczek *et al.*, 2009a). IFN-γ$^+$IL17$^+$ T cells have been reported in human tumours and in patients with autoimmune diseases (Kryczek *et al.*, 2008; Kryczek *et al.*, 2009a). Additionally Th17 cells have been reported to divert to Th1 under lymphopenic conditions in mice (Bending *et al.*, 2009; Martin-Orozco *et al.*, 2009a; Nurieva *et al.*, 2009). It is therefore speculated that in the tumour microenvironment Th17 cells may be gradually converted into Th1 mediating tumour rejection (Zou and Restifo, 2010).

A recent study by Martin-Orozco indicates that tumour specific Th17 cells play a protective role against tumours by triggering strong CD8 immune responses (Martin-Orozco *et al.*, 2009b). Th17 cells lack the ability to traffic to local regional lymph nodes (see above). However, Th17 cell therapy mediated DC recruitment in the tumour tissue in a CCL20/CCR6 dependent manner and further on the presentation of tumour antigens in tumour draining lymph nodes. The anti-tumour effects of Th17 were abrogated by CCR6 deficiency indicating the importance of the innate mediator. Notably, the Th17 cells retained their cytokine signature upon transfer in tumour bearing mice and exhibited stronger efficacy than Th1 cells. This finding suggests that tumour infiltrating Th17 cells may mediate protective immunity indirectly through DC recruitment and cytotoxic T cell activation.

Beside a pro- or anti-tumour function of Th17 cells clinical data from anti-CTLA4 treated melanoma patients has indicated that a post-dosing increase in Th17 cells within the

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peripheral blood mononuclear cell pool, associated with treatment-induced toxicity but not with an anti-tumour response (ribas 7 35) . Since Th17 cells have been so closely associated with inflammation and autoimmunity it is particularly important to investigate whether toxicities and responses could be differentially modulated in the context of cancer immunotherapy. The propagated plasticity of T cell populations is intriguing and the shift from Treg to Th17 cells might be beneficial in the right context.

Conclusions

The role of IL-17 and Th17 cells in the tumour microenvironment is not a clearcut case of pro- or anti-tumourigenic. The overall impact of IL-17 in cancer may also depend on other cellular sources of the cytokine, such as neutrophils, γδ T cells and NKT cells. Whether conventional anti-cancer therapies such as chemotherapy and radiotherapy modulate IL-17 secretion and/or Th17 polarisation and function is yet unexplored. Understanding the factors that regulate their pro- or anti-tumour activity will allow to use the functional properties of this exciting subpopulation for the development of more effective immune therapies in cancer.

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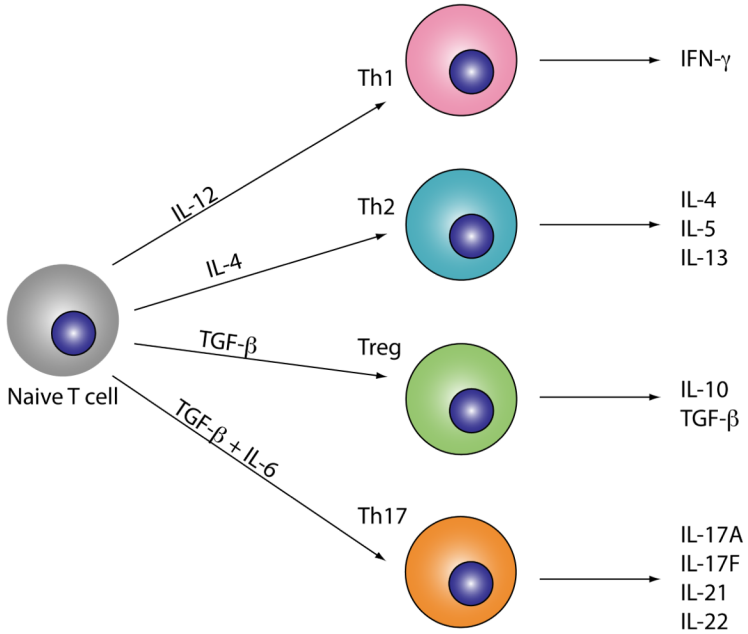

Figure 1. Differentiation of T cell subsets

Upon activation naïve $CD4^+$ T cells can differentiate into Th1, Th2, Th17 or Treg cells directed by the local inflammatory milieu. TGF-β and IL-6 induce Th17 cell polarisation characterised by the production of IL-17, IL-21 and IL-22 and the transcriptional factor RORγt.

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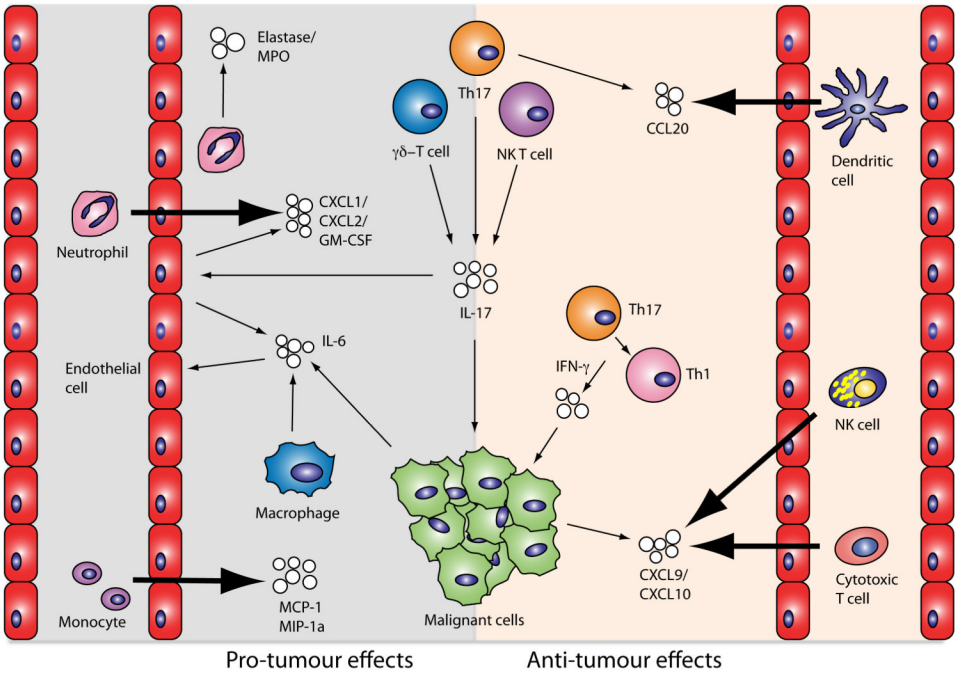

Figure 2. The pro and anti-tumour effects of Th17 cells and IL-17

Interleukin-17 derived from Th17 cells, γδ-T cells and NK T cells exerts pro-tumourigenic activites by a range of actions. It has direct effects on angiogenesis mediated by endothelial cells, it also has indirect angiogenic effects by stimulating them to release of IL-6. Furthermore, it induces endothelial cells to secrete CXC chemokines and growth factors resulting in the recruitment of neutrophils. Infiltrating neutrophils respond to IL-17 within the tumour microenvironment by releasing inflammatory proteinases. Other inflammatory cells, such as monocytes, are also attracted to the tumour site by IL-17 induced MCP-1 release by epithelial cells and fibroblasts, and subsequently mature to tumour associated macrophages. The anti-tumour effects of IL-17 primarily come through its ability, in conjunction with IFN-γ, to stimulate tumour cells to release the chemokines CXCL9 and CXCL10, which recruit NK cells and cytotoxic CD8 cells to the tumour. Th17 cells have also been demonstrated to release CCL20, a chemoattractant for dendritic cells, potentially leading to an enhanced immune response.

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Table 1

Immunopathological implications of IL-17 and Th17 cells in malignancies.

Pro-tumourigenic effects of IL-17		**References**
Immunocompromised mouse models	IL-17 overexpression in tumours leads to increased angiogenesis and tumour growth	(Numasaki *et al.*, 2003)
MB49 bladder adenocarcinoma and B16 melanoma model	Decreased tumour growth in IL-17$^{-/-}$ and IL-17R$^{-/-}$ mice	(Wang *et al.*, 2009; He *et al.*, 2010)
ID8 ovarian cancer model	TNF-dependent IL-17 release leads to increased myeloid cell recruitment and increased tumour burden	(Charles *et al.*, 2009)
Anti-tumourigenic effects of IL-17		
Immunocompetent mouse models	IL-17 overexpression in tumours leads to decreased tumour growth associated with increased CTL influx	(Benchetrit *et al.*, 2002)
MC38 colon cancer and B16-F10 melanoma model	Accelerated tumour growth in IL-17$^{-/-}$ mice	(Kryczek *et al.*, 2009b; Martin-Orozco *et al.*, 2009b)
Human ovarian cancer	IL-17 positively predicts survival	(Kryczek *et al.*, 2009a)
Th17 cells with potential pro-tumourigenic effects		
Gastric cancer	Blood Th17 cells increased in advanced cancer	(Zhang *et al.*, 2008)
Hepatocellular carcinoma	Increased Th17 cells in the tumour correlating with angiogenesis	(Zhang *et al.*, 2009)
Melanoma	Increased Th17 cells in the tumour	(Kryczek *et al.*, 2007)
Th17 cells with potential anti-tumourigenic effects		
Non-Hodgkin B-cell lymphoma	Tumours inhibit Th17 formation and promote differentiation towards Treg	(Yang *et al.*, 2009)
Prostate cancer	Responders to immunotherapy have higher levels of Th17 cells, inverse correlation between numbers of Th17 cells and tumour stage	(Sfanos *et al.*, 2008; Derhovanessian *et al.*, 2009)
Ovarian cancer	Reverse relationship between Th17 and Tregs	(Kryczek *et al.*, 2009a)
Breast cancer	Inverse correlation between Th17 and Treg cells following immunotherapy	(Horlock *et al.*, 2009)