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T_H17 cells in tumour immunity and immunotherapy

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Abstract

T helper 17 (T_H17) cells have well-described roles in autoimmune disease. Recent evidence suggests that this effector T cell subset is also involved in tumour immunology and may be a target for cancer therapy. In this Review, we summarize recent findings regarding the nature and relevance of T_H17 cells in mouse models of cancer and human disease. We describe the interplay between T_H17 cells and other immune cells in the tumour microenvironment, and we assess both the potential antitumorigenic and pro-tumorigenic activities of T_H17 cells and their associated cytokines. Understanding the nature of T_H17 cell responses in the tumour microenvironment will be important for the design of more efficacious cancer immunotherapies.

Although the link between inflammation and cancer has been noted for more than a century, investigators have only recently started to address the cellular, molecular and genetic causal relationships between these two events. Compelling evidence has shown that inflammation orchestrates the microenvironment around tumours, contributing to the proliferation, migration and survival of cancer cells that can result in tumour invasion, migration and metastasis. However, inflammatory reactions in the tumour microenvironment are an important component of the tumour-associated immune response. Inflammatory cells and molecules may have crucial roles in initiating and maintaining protective antitumour immunity. The specific nature of the inflammatory response and the tissue context may determine the beneficial versus the detrimental effects of inflammation on tumour pathology.

T helper 17 (T_H17) cells are an important inflammatory component and have been shown to promote inflammation in a number of autoimmune diseases[1–8]. Research on these cells is rapidly evolving, and recent reviews have extensively covered basic T_H17 cell biology, T_H17 cell lineage development and the relevance of T_H17 cells in autoimmune diseases [1–4,9,10]. In this Review, we summarize recent reports of T_H17 cells in patients with

Competing interests statement
The authors declare no competing financial interests.

DATABASES
UniProtKB: http://www.uniprot.org
CCR6 | CD39 | CD161 | CXCR4 | GM-CSF | IFNγ | IL-1β | IL-2 | IL-17 | RORγt | TNF

FURTHER INFORMATION
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cancer and in mouse tumour models. We examine the phenotype, recruitment, generation and function of tumour-associated T_H17 cells, focusing on their production of cytokines and on their interplay with other immune cells in the tumour microenvironment. Finally, we discuss the clinical relevance of T_H17 cells in tumour immunology and highlight their therapeutic potential.

T_H17 cells

Interleukin-17 (IL-17; originally termed CTLA8, also known as IL-17A) belongs to a family of six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F) and has been of great interest recently owing to the discovery that the production of IL-17 characterizes a subset of $CD4^+$ helper T cells (T_H17 cells). The development of T_H17 cells is distinct from the development of T_H1, T_H2 and regulatory T (T_{Reg}) cells and is characterized by unique transcription factors and cytokine requirements (FIG. 1). For further information on T_H17 lineage development, we refer the reader to some recent reviews[1–4,9].

Tumour-associated T_H17 cells

Tissue distribution

It is well appreciated that T_H17 cells contribute to autoimmunity[1–4]. However, one of the main physiological roles of T_H17 cells is to promote host defence against infectious agents, including certain bacteria, fungi, viruses and protozoa, and T_H17 cells are thought to be particularly important in maintaining barrier immunity at mucosal surfaces, such as the gut and lungs, as well as in the skin[11,12]. Consistent with this, T_H17 cells are highly prevalent in the mucosal tissues of healthy individuals[11,12].

More recently, T_H17 cells have been investigated in patients with diverse cancer types, including ovarian cancer and prostate cancer, and this list continues to grow (TABLE 1). A caveat of these studies is that most have examined T_H17 cells in peripheral blood, rather than in the tumour itself. However, it is generally agreed that although T_H17 cells may remain a minor population in the peripheral blood of patients with cancer, they can be more prevalent at the tumour site itself. Support for this has come from extensive study of the tissue distribution of T_H17 cells in patients with ovarian cancer. In these patients, the prevalence of T_H17 cells in tumour-draining lymph nodes and peripheral blood is similar to that found in the peripheral blood of healthy donors; however, higher proportions of T_H17 cells are found in tumours than at these other sites. This suggests that T_H17 cells may be induced in and/or recruited to the tumour microenvironment[13,14]. In addition to these studies from human cancers, T_H17 cells are also found in mouse tumour models. Consistent with the findings from human tumours, T_H17 cells are more prevalent in the mouse tumour tissue itself, although T_H17 cells are generally present at lower frequencies than other T cell subsets[13]. In summary, although not the predominant T cell subset within the tumour, T_H17 cells are present in the tumour microenvironment.

Expression of tissue-homing molecules

Human primary tumour-infiltrating T_H17 cells isolated from colon carcinomas, hepatocellular carcinomas, melanoma, ovarian carcinoma, pancreatic cancers and renal cell carcinomas express high levels of CXC-chemokine receptor 4 (CXCR4), CC-chemokine receptor 6 (CCR6), several CD49 integrins and the C-type lectin receptor CD161 (also known as KLRB1), but do not express CD62L or CCR7 (REF. 14). This suggests that these T_H17 cells do not home to lymphoid tissues, but some of the above homing molecules might be involved in T_H17 cell migration to, and retention within, inflammatory tissues and tumours[14–17]. For example, high levels of CXC-chemokine ligand 12 (CXCL12) (the ligand for CXCR4)[18,19] and CCL20 (the ligand for CCR6)[20] are found in human tumour micro-

environments. Therefore the expression of CXCR4 and CCR6 could facilitate T_H17 cell trafficking to tumours. However, these molecules are not exclusively expressed by tumour-infiltrating T_H17 cells; high levels of CCR6 and CD161 are expressed by T_H17 cells isolated from healthy donors[21], as well as by non-T_H17 cells from tumours and other inflamed tissues[22]. Therefore, to date, there are no known specific chemokine receptors or homing molecules associated with T_H17 cells in the tumour environment. As such, there are no specific markers for identifying and isolating these T_H17 cells for functional experiments.

Activation markers

Conventional effector T cells often express HLA-DR, CD25 and granzyme B, but tumour-infiltrating T_H17 cells have been shown to express negligible levels of these molecules[14]. This suggests that these T_H17 cells might not be conventional effector T cells and might not mediate effector functions through the granzyme B pathway. In addition, T_H17 cells express minimal levels of programmed cell death 1 (PD1) and forkhead box P3 (FOXP3) suggesting they do not contribute to immune suppression in the tumour microenvironment[14]. Therefore, T_H17 cells seem to be distinct from T_{Reg} cells and other effector T cells present in the tumour.

Cytokine profile

Tumour-infiltrating T_H17 cells express other cytokines in addition to IL-17, and this might be functionally relevant in several physiological and pathological settings. Human tumour-infiltrating T_H17 cells express negligible levels of the anti-inflammatory cytokine IL-10, but around 50–90% of T_H17 cells produce high levels of effector cytokines such as IL-2, granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ) and tumour necrosis factor (TNF)[14]. Following culture under T_H17-polarizing conditions, mouse $CD4^+$ and $CD8^+$ T cells have been shown to express IFNγ *in vitro* and also *in vivo* following transfer into irradiated mice[15,23]. Therefore, tumour-associated T_H17 cells exhibit an effector T cell cytokine profile similar to that of effector T cells that have been described in infectious diseases[24,25]. A similar cytokine profile has been observed in T_H17 cells associated with distinct human tumour types, including carcinomas of the skin, intestine, pancreas, liver and ovaries[14] (TABLE 1). These data indicate that T_H17 cells might have a protective role in tumour immunopathology by promoting antitumour immunity.

T_H17 cell interactions in the tumour

T_H17 cells and antigen-presenting cells

It is not known whether tumour-associated T_H17 cells are induced in the tumour microenvironment itself or if they are recruited from distal sites. Antigen-presenting cells (APCs), such as dendritic cells, induce T cell polarization into different effector T cell subsets (FIG. 1). Although tumour-associated plasmacytoid dendritic cells isolated from ovarian cancers had minimal effect on T_H17 cell induction, tumour-associated macrophages and myeloid dendritic cells stimulated IL-17 production from memory T cells but not from naive T cells[14,16,26]. In addition, tumour-associated macrophages were shown to be more efficient than normal macrophages in eliciting T cell IL-17 production[14,26]. As macrophages outnumber myeloid dendritic cells in many human cancers[18,27] and are superior to myeloid [14,26], macrophages dendritic cells in inducing T_H17 cells might be the main inducers of T_H17 cells in the human tumour microenvironment.

Consistent with this possibility, tumour-associated macrophages expressed higher levels of IL-1β than normal tissue macrophages and normal monocyte-derived macrophages[14,28]. IL-1β, but not IL-1α, IL-6, IL-23 or transforming growth factor-β (TGFβ), is crucial for T_H17 cell induction by human tumour-associated myeloid APCs[14]. Consistent with this

observation, the levels of IL-1α and IL-23 are negligible in ovarian cancer ascites[14]. As IL-1α, IL-1β and IL-23 are involved in memory T_H17 cell expansion in patients with psoriasis[16,26], it is possible that the molecular mechanisms involved in inducing T_H17 cells in patients with tumours are different from those in patients with autoimmune diseases. The involvement of IL-6 and TGFβ in human T_H17 cell development remains controversial. It is suggested that TGFβ is essential for human T_H17 cell development [29–31]. However, high concentrations of TGFβ promote the development of T_{Reg} cells and suppress T_H17 cell differentiation [29,30,32,33]. High levels of IL-6 and TGFβ are often detected in the tumour microenvironment[34]. Therefore, if IL-6 and TGFβ have potent roles in promoting T_H17 cell induction, one might expect substantial numbers of T_H17 cells in human tumours. However, compared with the numbers of T_{Reg} cells and other T cell subsets, the numbers of T_H17 cells present in both human and mouse tumours are limited[13]. Blockade of IL-1β, but not IL-6 or TGFβ, decreases T_H17 cell induction by myeloid APCs isolated from patients with ovarian cancer[14]. Furthermore, the levels of IL-17 and numbers of T_H17 cells do not correlate with IL-6 and TGFβ levels in patients with ovarian cancer[14]. Therefore, only IL-1β, but not IL-6 or TGFβ, seems to be crucial for T_H17 cell development in the ovarian cancer microenvironment. Recent mouse studies also support a crucial role for IL-1β in promoting T_H17 cell development[5,35–37].

Thus, myeloid APCs can induce T_H17 cells in the human tumour microenvironment through IL-1β production[14], but T_H17 cells in turn promote dendritic cell trafficking into tumour-draining lymph nodes and the tumour environment by producing CCL20. This chemokine can lead to the recruitment of dendritic cells to the tumour in a CCR6-dependent manner[17]. As human T_H17 cells also express high levels of CCR6 (REFs 14,16) and efficiently migrate towards CCL20 (REF. 16), T_H17 cells might increase their own frequency in the tumour by both direct and indirect mechanisms.

T_H17 and T_{Reg} cells

As already mentioned, fewer T_H17 cells are found in the tumour microenvironment than cells and other effector T cell subsets[14,38]. Interestingly, T_{Reg} the numbers of T_{Reg} and T_H17 cells are inversely associated in the same tumours[13,14]. This suggests that there could be a dynamic interaction between T_H17 and T_{Reg} cells in the tumour microenvironment. Consistent with this possibility, mouse peripheral mature T_{Reg} cells can be converted into T_H17 cells; this event is favoured by inflammation and IL-6 production[10,39,40]. In addition, IL-17^+FOXP3^+ T cells can be detected in humans[41,42]. However, it is not known whether these IL-17^+FOXP3^+ T cells originate from T_H17 cells or from T_{Reg} cells. These IL-17^+FOXP3^+ T cells also express CD25 and the T_H17 lineage specific transcription factor retinoic acid receptor-related orphan receptor-γt (RORγt), and have suppressive functions. This indicates that IL-17^+FOXP3^+ cells have certain functional characteristics of T_{Reg} and T_H17 cells. Notably, despite the high levels of IL-6 detected in some human epithelial cancers[34,43], the number of T_H17 cells is limited in the tumour microenvironment; therefore, the positive effect of IL-6 in inducing T_H17 cells might be subverted by an unidentified mechanism. Interestingly, in the presence of retinoic acid, which enhances TGFβ signalling and inhibits IL-6 signalling, IL-6 could not induce IL-17 production from FOXP3^+ T cells[39]. However, it is unknown whether retinoic acid affects the balance between T_{Reg} and T_H17 cells in the tumour microenvironment. Nonetheless, the plasticity of the T_{Reg} cell lineage might allow the initial skewing of T_{Reg} cells towards an IL-17^+FOXP3^+ phenotype[10] and eventually into potentially protective FOXP3^- T_H17 cells that can promote antitumour immunity.

Then why are there limited numbers of T_H17 cells in tumours? Although tumour-associated macrophages are potent T_H17 cell inducers *in vitro*, tumour-associated T_{Reg} cells express high levels of CD39 (also known as NTPDase 1), an ectonucleotidase that converts ATP

into adenosine, which suppresses T_H17 cell development through the adenosinergic pathway[14]. Supporting this hypothesis, it has been reported that mouse T_{Reg} cells can use this pathway to suppress T cell activation[44,45] and T cell-mediated protective immunity[46]. It was also reported that mouse T_{Reg} cells inhibit T_H17 cell responses *in vivo* in a signal transducer and activator of transcription 3 (STAT3)-dependent manner, and T_{Reg} cell-specific ablation of STAT3 leads to the loss of their suppressive functions[47]. If T_H17 cells mediate protective immunity, inhibition of T_H17 cell development could be a previously unappreciated mechanism by which tumours evade the immune system[14].

T_H17 and T_H1 cells

Although there are no experiments directly demonstrating the lineage association between T_H17 and T_H1 cell development, there is evidence indicating that T_H17 cells and T_H1 cells might be phenotypically, developmentally and functionally linked in the tumour microenvironment[48]. IFNγ, a typical T_H1-type cytokine, is expressed by primary T_H17 cells in human tumours[14] and T_H17-polarized mouse cells [15]. IFNγ^+IL-17$^+$ T cells are also found in patients with autoimmune diseases[16]. It is possible that IFNγ^+IL-17$^+$ T cells can develop from T_H1 cells and/or T_H17 cells [49]. Consistent with this, adoptive transfer of antigen-specific IL-17$^+$CD8$^+$ T cells into antigen-bearing hosts results in their conversion to IFNγ^+CD8$^+$ T cells[50]. In mouse models, under lymphopenic conditions, T_H17 cells can redifferentiate into T_H1 cells [51–53]. Given that after chemotherapy and radiotherapy, patients with cancer might mimic lymphopenic hosts, and given that there are substantial numbers of IFNγ^+IL-17$^+$ T cells[14], T_H17 cells could initially express low levels of IFNγ but gradually be converted into T_H1 cells *in vivo*. However, although IFNγ inhibits T_H17 cell differentiation from naive T cells in mice, T_H1 cell-derived IFNγ might drive APCs to promote memory T_H17 cell expansion through inducing the production of IL-1 and IL-23 by APCs[16,26].

The functional interaction between T_H1 cells and T_H17 cells has been appreciated in human tumours [14], mouse immunotherapeutic settings[15,17,23] and auto-immune disease models[16,26,54,55]. This interaction might contribute to antitumour immunity, and is functionally relevant and therapeutically meaningful.

T_H17 cells and antitumour immunity

Evidence for antitumour activity

The relationship between T_H17 cells and tumour immunopathology has been controversial[56–58]. However, there are several lines of evidence suggesting that T_H17 cells can promote protective antitumour immune responses. Firstly, tumour-infiltrating T_H17 cells express several effector cytokines, similar to that observed in patients with infectious diseases[24,25]. This suggests that tumour-associated T_H17 cells might be functional effector T cells. Consistent with this possibility, T_H17 cells are negatively correlated with the presence of T_{Reg} cells[14,38] and are positively correlated with effector immune cells, including IFNγ^+ effector T cells, cytotoxic CD8$^+$ T cells and natural killer (NK) cells, in the same tumour microenvironment[14]. These observations are supported by data from both human and mouse tumours[14,17,59].

Transgenic T cells polarized to a T_H17 cell phenotype following treatment with TGFβ and IL-6 were shown to induce tumour eradication in mice[15,17,23]. In addition, IL-17-deficient mice show accelerated tumour growth and lung metastasis in many tumour models, and forced expression of IL-17 in tumour cells was shown to suppress tumour progression[17,59–62]. Furthermore, immunotherapies associated with enhanced T_H17 cell activity, such as blocking indoleamine 2,3-dioxygenase (IDO)[63], treatment with IL-7 (REF.

64) or vaccination with heat shock protein 70 (HSP70)[65], resulted in improved antitumour immunity.

In patients with prostate cancer, a significant inverse correlation is found between T_H17 cell differentiation and tumour progression[66]. Treatment with specific antibody against cytotoxic T lymphocyte antigen 4 (CTLA4)[67] induces T_H17 cells in patients with melanoma and the levels of IL-17 detected in tumour-associated ascites positively predicts patient survival. Taken together, these data provide strong evidence that T_H17 cells can have protective roles in tumour immunity.

Mechanisms of antitumour activity

How do T_H17 cells mediate antitumour immunity in patients with cancer? Human T_H17 cells, including T_H17 cells found in tumours, do not express granzyme B or perforin and have no direct effects on primary ovarian cancer cell proliferation and apoptosis. Therefore T_H17 cells may not mediate direct cytotoxic activity against tumour cells[14,50]. Instead, T_H17 cells might mediate their antitumour activity indirectly, by facilitating the recruitment of other effector immune cells[68–70]. Consistent with this hypothesis, IL-17 was positively associated with tumour-infiltrating IFNγ^+ effector T cells[14]. Mechanistically, T_H17 cell-derived IL-17 and IFNγ synergistically induced the production of the T_H1-type chemokines CXCL9 and CXCL10 by tumour cells, which in turn promoted effector T cell migration towards tumours[14]. Levels of CXCL9 and CXCL10 were found to directly correlate with the number of tumour-infiltrating $CD8^+$ T cells and NK cells. These data strongly suggest that T_H17 cells have an indirect role in antitumour immunity by promoting effector T cell and NK cell trafficking to, and retention within, the tumour microenvironment (FIG. 2).

T_H17 cell-mediated antitumour activity could also be linked to dendritic cell recruitment into the tumour microenvironment or into tumour-draining lymph nodes. As mentioned above, T_H17 cells can stimulate CCL20 expression in tumour tissues and promote dendritic cell tumour trafficking in a CCL20–CCR6 dependent manner. In turn, $CD8^+$ T cells are effectively primed and activated by dendritic cells and mediate potent antitumour immune responses. Altogether, these data suggest that T_H17 cells might not mediate direct anti-tumour activity, but can promote antitumour immunity indirectly through the recruitment of dendritic cells and cytotoxic effector cells[17] (FIG. 2).

Pro-tumour role of T_H17 cell-associated cytokines

IL-17 and T_H17 cells

Although IL-17 is the signature cytokine of T_H17 cells, the production of IL-17 is not the sole function of T_H17 cells. Thus, the biological activities of IL-17 should not be equated with the biological activities of T_H17 cells (BOX 1). In addition to leukocytes of the immune system, the cellular targets of IL-17 in the tumour microenvironment can be vascular endothelial cells, stromal cells and cells of the tumour itself. Early studies showed that exogenous IL-17 could promote tumour growth by inducing tumour vascularization, particularly in immune-deficient nude mice and severe combined immunodeficient (SCID) mice[71–73] (TABLE 2). However, the overall effect of IL-17 on tumour development and growth might be different in immune-competent hosts, as shown by the potent antitumour effects mediated by IL-17 in immune-competent mice[60,61] (TABLE 2). Furthermore, as a result of differences in local concentrations, bioavailability and potential targets, the biological activities of endogenous IL-17 (such as IL-17 derived from T_H17 cells) and exogenously administered IL-17 might differ. Two recent reports have shown that, in mice, endogenous IL-17 promotes *Bacteroides fragilis*-induced tumour formation[74] and tumour growth in a transplanted tumour model[75]. IL-17 induces IL-6 production by tumour cells and tumour-associated stromal cells, which in turn activates STAT3, an oncogenic

transcription factor that upregulates pro-survival and pro-angiogenic genes[75]. Furthermore, although IL-17 deficiency leads to increased numbers of IFNγ-producing NK cells in the tumour-draining lymph nodes of tumour-bearing mice[59], it has also been reported that IL-17 can decrease NK cell activity in a mouse model of dermatitis[76]. Therefore IL-17 can promote tumour growth in certain tumour-bearing mouse models, and the effects of IL-17 on tumour growth might be highly context dependent (BOX 1; TABLE 2).

IL-23 and T_H17 cells

IL-23 is an IL-12 cytokine family member, which is produced by APCs and promotes the expansion and survival of T_H17 cells. It has been reported that IL-23-deficient mice are resistant to chemically induced tumours[77]. This resistance is associated with decreased expression of matrix metal-loproteinase 9 (MMP9) in the skin, a decrease in the expression of angiogenic markers and high levels of $CD8^+$ T cell infiltration. Given the close relationship between IL-23 and T_H17 cells, it has been proposed that T_H17 cells or IL-17 derived from T_H17 cells can promote tumorigenesis in this model.

However, this hypothesis remains to be tested and antitumour effects of IL-23 have been observed in several mouse tumour models[78–82]. Vaccination with IL-23-transduced dendritic cells[78] or overexpression of IL-23 at tumour sites has been shown to result in a robust infiltration of $CD8^+$ T cells to the tumour and inhibition of tumour growth[79–81]. In addition, systemic administration of IL-23 suppressed the growth of a pre-existing fibrosarcoma in mice and resulted in increased survival[82]. Altogether, these data indicate that IL-23 might have distinct roles in antitumour immune responses and can either promote or inhibit tumorigenesis depending on the context of the experimental conditions (BOX 1; TABLE 2).

Targeting T_H17 cells for cancer therapy

The involvement of T_H17 cells in the pathogenesis of various autoimmune diseases has been reviewed elsewhere[1–8,10]. It has been argued that cancer rejection can be viewed as intentional induction of autoimmune disease[83]. The antitumour activities of $CD8^+$ T cells have received the most attention in the field of tumour immunology; these cells produce IFNγ, GM-CSF and TNF and can specifically lyse antigen-presenting MHC class I^+ tumours. The infusion of large numbers of tumour-specific $CD8^+$ T cells, expanded *in vitro* with IL-2, can induce the regression of large tumour burdens in mice and in humans[84]. However, the use of $CD4^+$ helper T cell subsets in tumour immunotherapy has been under-explored, especially in the clinic. This can be attributed partly to the massive diversity of the MHC class II loci and partly to the complexity of $CD4^+$ helper T cell subtypes in mice and humans. Initial studies focused on the potential for helper $CD4^+$ T cells to promote $CD8^+$ T cell responses by enhancing their activation and persistence in the tumour environment. However, it soon became clear that suppressive immune networks, such as T_{Reg} cells, could suppress APCs and other tumour associated-immune responses and dramatically inhibit the antitumour response[34,85–90].

In early experiments, both T_H1 and T_H2 cell subsets were shown to have some antitumour activity, but the IFNγ-secreting T_H1 cells were thought to be the more efficacious at tumour destruction[48]. T_H17 cells generated under the influence of TGFβ and IL-6 (and, more recently, expanded by cytokine cocktails) have been found to be highly effective in triggering the eradication of large, established tumours in mice[15]. Effective antitumour T_H17 cells are less prone to apoptosis than their T_H1 cell counterparts, although the reasons for this are not completely understood.

Although IL-17-secreting $CD8^+$ T cells are not $^+CD8^+$ T cells can be polarized using T_H17 cells, IL-17 a T_H17-inducing cytokine cocktail, and their potential roles in cancer immunotherapy have been explored in two recent publications[23,50]. IL-17-producing $CD8^+$ T cells have greatly enhanced expression of RORγt, decreased expression of eomesodermin and their canonical cytotoxic activity is diminished. Like their $CD4^+$ counterparts, these $CD8^+$ T cells can acquire the ability to produce IFNγ and mediate regression of large, established tumours. This enhanced antitumour activity is associated with increased *in vivo* expansion and persistence of the transferred cells. Type 17-skewed $CD8^+$ T cells have decreased expression of killer cell lectin-like receptor G1 (KLRG1), a marker of $CD8^+$ T cell senescence, and also show increased expression of IL-7Rα, a cytokine receptor associated with memory T cell formation. This evidence suggests that the skewing of both $CD8^+$ T cells and $CD4^+$ T cells towards an IL-17-producing phenotype improves their antitumour activity.

Efforts to use polarized helper T cell subsets in the clinic to induce tumour regression have been minimal. Although a single case study reported a dramatic antitumour response in a patient treated with *ex vivo* generated autologous $CD4^+$ T cell clones, which recognized the tumour-associated antigen NY-ESO1 (REF. 91), these cells were not specifically polarized to any helper T cell subset. Based on the data from animal models, the treatment of patients with cancer with T_H17-polarized T cells seems to be a promising approach; however, at the time of writing, there have been no published reports on the use of T_H17 cells to treat any human cancer. Given our knowledge of human tumour systems, it seems plausible that a clinical trial involving the adoptive transfer of T_H17-polarized, tumour-specific T cells could be carried out. One credible trial design involves the polarization of naive human T cells using a cocktail of cytokines, such as IL-1β, IL-6, IL-21, IL-23, TGFβ and TNF[92]. Recombinant gammaretroviruses or lenti-viruses that encode genes for tumour antigen-specific T cell receptors or chimeric antigen receptors could be used to confer antitumour activity onto autologous, T_H17-polarized T cells. Similar to the strategy that has been used for genetically engineered $CD8^+$ T cells, the resulting T_H17 cells could be expanded to large numbers *in vitro* and then transferred back into patients with cancer[93].

Concluding remarks

Despite the recent identification of T_H17 cells, over the past few years we have made rapid and large advances in our understanding of the development, regulation and function of these cells. This has been particularly true in the context of autoimmune diseases, where the pathogenic role of T_H17 cells has been well documented. However, the exact nature of T_H17 cells in antitumour immunity is not a 'black and white' picture: the roles of T_H17 cells in tumorigenesis are best represented by many colours. T_H17 cells and T_H17-associated cytokines have been shown to have both antitumorigenic and pro-tumorigenic functions. Therefore, the relationship between T_H17 cells and tumour immunopathology are highly dependent on context (BOX 1), but a better understanding of these contexts could be used to develop and refine new cancer therapies.

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Glossary

Regulatory T (T_{Reg}) cells	A specialized subset of CD4+ T cells that can suppress inflammation and the responses of other T cells. These cells provide a crucial mechanism for the maintenance of peripheral self tolerance. A subset of these cells is characterized by expression of CD25 and the transcription factor FOXP3
Granzyme B	A secreted serine protease that enters target cells through perforin pores, it then cleaves and activates intracellular caspases, leading to target-cell apoptosis
Plasmacytoid dendritic cells	A subset of dendritic cells that is described as plasmacytoid because their microscopic appearance resembles plasmablasts. In humans, these cells can be derived from lineage-negative stem cells in peripheral blood and are the main producers of type I IFN in response to virus infections
Indoleamine 2,3-dioxygenase	(IDO). An intracellular haeme-containing enzyme that catalyses the oxidative catabolism of tryptophan. Insufficient availability of tryptophan can lead to T cell apoptosis and anergy
Cytotoxic T lymphocyte antigen 4	(CTLA4). A T cell surface protein that, following its ligation by CD80 or CD86 on antigen-presenting cells, delivers a negative signal to activated T cells. This induces cell cycle arrest and inhibits cytokine production. CTLA4 is constitutively expressed by, and functionally associated with, regulatory T cells

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Box 1

T_H17 cell biology and important research contexts

The biological activities of T helper 17 (T_H17) cells and the T_H17 cell-associated cytokines (interleukin-17 (IL-17) and IL-23) may be highly context dependent. The following aspects could be crucial for our understanding of the antitumour versus pro-tumour activities of IL-17 and/or T_H17 cells.

Exogenous versus endogenous Il-17

The findings that IL-17 can have pro-tumorigenic or antitumorigenic activity might be due, in part, to the source of IL-17 in each of the studies. Exogenously delivered IL-17 might differ in dose from endogenous IL-17 that is produced by T_H17 cells and other IL-17-expressing cells. Therefore, the biological activities of exogenous versus endogenous IL-17 might not be identical (TABLE 2).

Il-17$^+$ cell populations

IL-17 can be produced by T_H17 cells, CD8$^+$ T cells, natural killer T (NKT) cells and osteoclasts[1–4,104]. The biological activities of IL-17 made by different cell types may not be identical owing to the different levels of IL-17 and other contexts, including localization, cytokine profile and cellular environments.

T_H17 cell subsets

Both IL-10$^+$ and IL-10$^-$ T_H17 cell subsets can be detected in mice. Although they both express IL-17, it has been reported that IL-10$^-$ but not IL-10$^+$ T_H17 cells are pathogenic in experimental autoimmune encephalomyelitis (EAE) models[105–107]. Furthermore, there are IL-17$^+$CD8$^+$ T cells. Current evidence indicates that IL-17$^+$CD8$^+$ T cells might be functionally similar to T_H17 cells in certain settings[17–23].

T_H17 cell cytokine profile

The function of T_H17 cells may not be solely determined by IL-17. In addition to IL-17, tumour T_H17 cells can express many cytokines, including IL-2, IL-9, IL-22, granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ) and tumour necrosis factor (TNF)[14,15,23]. These cytokines may synergize with IL-17 to mediate biological activities. For example, IFNγ and IL-17 derived from T_H17 cells synergistically induce β-defensin 2 and T_H1-type chemokines[14,16].

T_H17 cells and associated cytokines

Several cytokines are associated with T_H17 cell development. The role of IL-23 is controversial in the context of tumour pathology. Although IL-23 is involved in regulating T_H17 cell development, the biological activities of IL-23 should not necessarily be associated with only T_H17 cell activity[77–82] (TABLE 2).

Cellular targets

IL-17 and T_H17 cells can target tumour cells, stromal cells, vascular endothelial cells and immune cells [14–17,60,61,71–73]. The functional activities of IL-17 may be determined by the net effects of IL-17 on different cellular targets.

Research models

The research models can be human subjects or animals, immune-competent or immune-deficient hosts, and subjects with or without chemical or infection-associated inflammation. The role of IL-17 in tumorigenesis might depend on the research model

used. For example, IL-17 can be pro-tumorigenic in immune-deficient models[71–73] but has been shown to have antitumorigenic properties in immune-competent models[60,61].

Disease stages

Human tumorigenesis is often a slow process that occurs over many years. Immune responses are likely to be dynamically altered in the tumour microenvironment at different stages of tumour development[14,66]. Mouse tumour models may not represent a satisfactory model for dissecting the nature of human tumours at specific stages (TABLEs 1, 2). Presumably, the predominant role of IL-17 and T_H17 cells can vary at different stages of tumorigenesis [14,66,74,75].

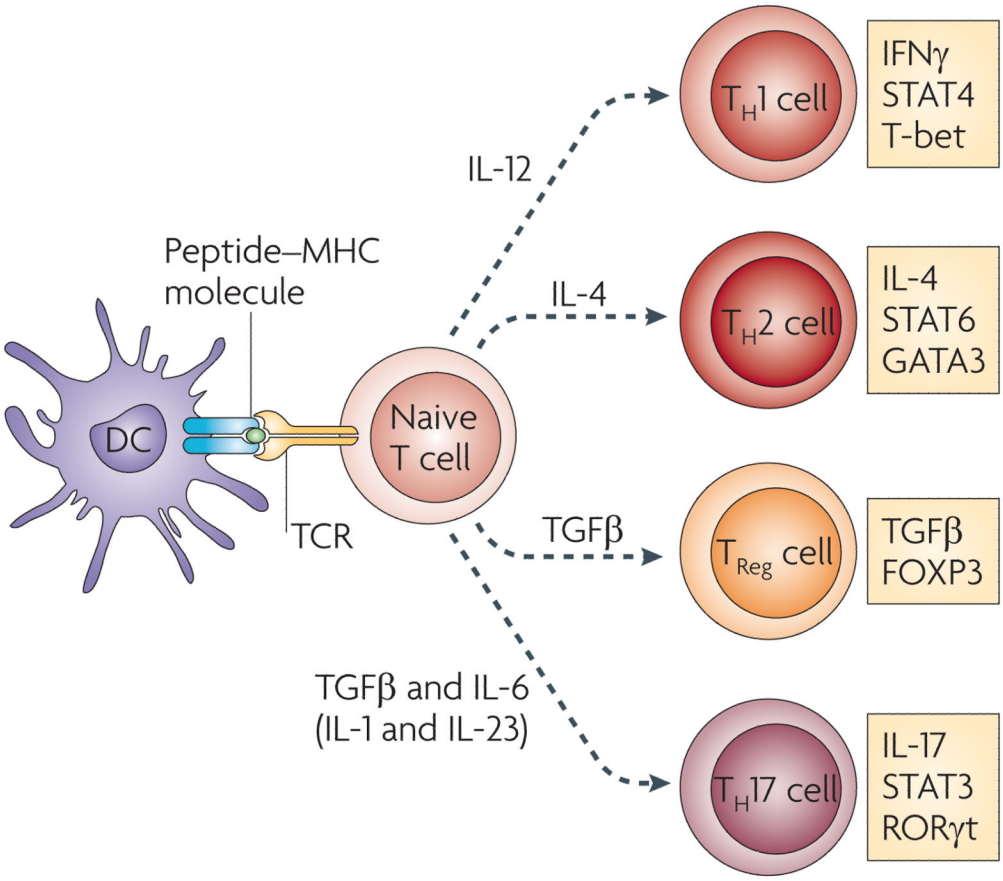

Figure 1. Differentiation of helper T cell subsets

Following activation by antigen-presenting cells such as dendritic cells (DCs), naive $CD4^+$ T cells can be polarized into different effector T cell subsets — T helper 1 (T_H1), T_H2, T_H17 and regulatory T (T_{Reg}) cells — depending on the local cytokine environment. The differentiation of each of these effector T cell subsets is controlled by distinct sets of transcription factors. In the presence of interleukin-6 (IL-6) and transforming growth factor-β (TGFβ), naive T cells can differentiate into T_H17 cells, which are characterized by expression of the transcription factors retinoic acid receptor-related orphan receptor-γt (RORγt) and signal transducer and activator of transcription 3 (STAT3). Furthermore, IL-1 and IL-23 can promote and/or stabilize T_H17 cell differentiation and expansion. FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; IFNγ, interferon-γ; TCR, T cell receptor.

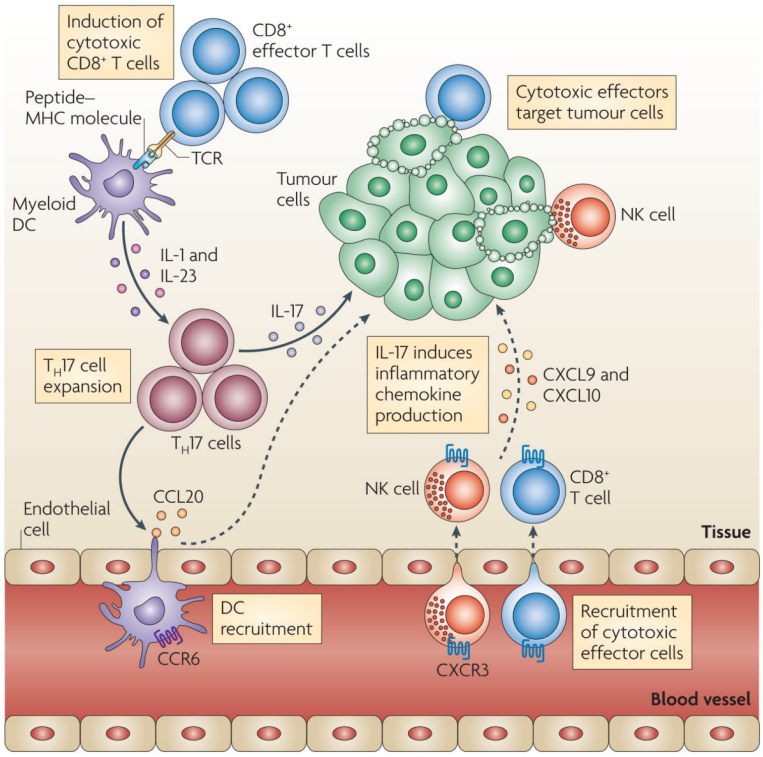

Figure 2. T_H17 cells and antitumour immunity

T helper 17 (T_H17) cells traffic to the tumour microenvironment and are expanded by antigen-presenting cells, such as myeloid dendritic cells (DCs) through interleukin-1 (IL-1) and IL-23. T_H17 cells promote the trafficking and retention of effector T cells and natural killer (NK) cells in the tumour environment, through inducing the production of the chemokines CXC-chemokine ligand 9 (CXCL9) and CXCL10 by primary tumour cells. In addition, T_H17 cells induce the production of CC-chemokine ligand 20 (CCL20) by tumour cells and this leads to the recruitment of CC-chemokine receptor 6 $(CCR6)^+$ DCs. Therefore T_H17 cells can promote protective antitumour immunity by inducing the recruitment of pro-inflammatory immune effector cells; TCR, T cell receptor.

Table 1

T_H17 cells in human carcinomas: immunological, clinical and pathological associations

Human cancer type	Presence of T_H17 cells	Effects associated with the presence of T_H17 cells	Refs
B cell (non-Hodgkin) cancer	Limited T_H17 cells in the tumour	Tumours inhibited T_H17 cell formation and promoted T_{Reg} cells through IL-2	94
Breast cancer	Fewer T_H17 cells in blood in $HER2^+$ than $HER2^-$ patients	Reverse relationship between T_H17 and T_{Reg} cells; trastuzumab* decreased T_{Reg} cells and increased T_H17 cells	95
Colon cancer	T_H17 cells detected in the tumours	Polyfunctional T_H17 cells present	14
Gastric cancer	T_H17 cells detected in blood and *IL17*mRNA in the tumour	Blood T_H17 cells and IL-17 increased in advanced cancer	96
Hepatocellular cancer	Increased T_H17 cells in the tumour	Polyfunctional T_H17 cells; T_H17 cells correlate with angiogenesis in viral hepatitis associated carcinoma	14,97
Melanoma	Increased T_H17 cells in the tumour	Polyfunctional T_H17 cells. IFNα2 increased T_{Reg} cells, but not T_H17; tremelimumab‡ increased T_H17 cells	14,67,98
Myeloma	Bone marrow	Polyfunctional T_H17 cells; DCs induce T_H17 cells	99
Ovarian cancer	Increased T_H17 cells in the tumour	Polyfunctional T_H17 cells negatively correlated with T_{Reg} cells; tumour IL-17 levels positively predict survival	13,14,28,100
Pancreatic cancer	Increased T_H17 cells in the tumour	Polyfunctional T_H17 cells in the tumour	14
Prostate cancer	Increased T_H17 cells in the tumour	T_H17 cells were higher in those responsive to immunotherapy than in non-responders and negatively correlated with stages	66,101
Renal cell cancer	Increased T_H17 cells in the tumour	Polyfunctional T_H17 cells in the tumour	14,102
Small cell lung cancer	Increase in number of peripheral T_H17 cells	Higher levels of peripheral T_H17 cells are observed in patients with limited-stage disease and in long-term survivors	103

DC, dendritic cell; HER2, human epidermal growth factor receptor 2; IFN, interferon; IL, interleukin; T_H17, T helper 17; T_{Reg} cell, regulatory T cell.

*Herceptin; Genentech/Roche.

‡Pfizer/Medarex.

Table 2

Antitumour and pro-tumour activities of IL-17 and IL-23

Cytokine	model system	Antitumour or pro-tumour effects	Refs
IL-17	Nude or SCID mice	Enhanced tumour vascularization and tumour growth	71–73
	Immune-competent mice	Enhanced antitumour immunity	60,61
IL-23	IL-23-deficient mice	Reduced MMP9 expression, tumour angiogenesis and fewer chemically-induced tumours	77
	IL-23-transfected B16F10 cells	Enhanced antitumour immunity; the effects are IFNγ and/or $CD8^+$ T cell dependent	78
	IL-23-transduced DCs		81
	IL-23-expressing bone marrow cells		79
	Liver IL-23 overexpression and gp100-specific T cells		80
	Systemic IL-23 treatment		82

DC, dendritic cell; IFNγ, interferon-γ; IL, interleukin; MMP9, matrix metalloproteinase 9; SCID, severe combined immunodeficient.