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T_H17 Cells in Cancer Related Inflammation

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1. Introduction

Until 2005, T helper (CD4+) cells were proposed to be a binary system, consisting of T_H1 and T_H2 cells (Mosmann TR *et al.*,1986) , when a third T helper -cell subset, known as T_H17 (interleukin-17 (IL-17) expressing cells), was identified (Harrington LE *et al.,* 2005, Park H *et al.,* 2005). This was followed up by the another independent discovery in three different laboratories of the differentiation factors cytokines such as interleukin (IL)-6 and transforming growth factor beta (TGF-β), that simplified *in vitro* analysis of this T cell subset to a large extent (Veldhoen M *et al.,* 2006, Bettelli E *et al.,* 2006, Mangan *et al.,* 2006). The discovery of these unique T_H17 cells has opened up exciting new avenues for research into the etiology and therapeutics of a broad spectrum of human diseases and data on the biology of these cells have emerged at an astounding pace in just 5 years. The reason for these cells to receive considerable attention in these recent years is their emerging involvement as principal mediators of pathogenesis in several autoimmune and chronic inflammatory disorders. Many reviews of the field have already highlighted the important role of T_H17 cells in the diverse group of human autoimmune and inflammatory diseases (Tesmer *et al*., 2008, Sallusto and Lanzavecchia 2009, Torrado and Cooper 2010, Kimura and Kishimoto 2011, Cosmi *et al.,* 2011).

With regards to cancer, the involvement of T_H17 cells in tumour immunology has raised their status as a target for cancer therapy. However based on the reported evidence on the potential anti-tumourigenic and pro-tumourigenic activities of T_H17 cells, their role as friends or foes, respectively is still under debate; could be because of a few studies have focused on primary T_H17 cells in the human tumour microenvironment (Wilke *et al.,* 2011). The link between cancer development and inflammation is now widely accepted and cancer patients have local and systemic changes in inflammatory parameters (Chechlinska, *et al.,* 2010). Tumours frequently display the characteristics of chronically inflamed tissue, including immune cell infiltration and an activated stroma (Kanwar *et al.,* 2008, Mantovani *et al.,* 2008*)*. Indeed inflammation has been proposed as the seventh trait of cancer by supplementing Hanahan and Weinberg's model that identifies six hallmarks of cancer (Mantovani 2009). This chapter focuses on the role of T_H17 cells in cancer by understanding its links with chronic inflammation.

2. Association of cancer with inflammation

Inflammation is the first line of defence against various extracellular stimuli (microbes, trauma, chemicals, heat or any other phenomenon) and can be acute or chronic. Acute or physiological inflammation is when body cells respond to external stimuli for short periods of time. Normal inflammation, for example, inflammation associated with acute infections, injury, wound healing is usually self-limiting; however, dysregulation of any of the involved factors leads to abnormalities. If the stimulus sustains for longer time, it results in a pathological state known as chronic or pathological inflammation as seen in autoimmune and chronic inflammatory diseases such as atherosclerosis, multiple sclerosis, rheumatoid arthritis, allergic inflammation of the lung leading to asthma (Kanwar *et al.,* 2001a, Kanwar 2005, Kanwar *et al.,* 2008, Kanwar *et al.,* 2009, Barreiro *et al.,* 2010). Chronic inflammation is also the case during tumour progression in cancer. The patients with chronic inflammatory conditions have a greatly increased risk of cancer in the affected organs. Also chronic inflammation resulting from viral or bacterial infections can often lead to or hasten the development of malignancy (Coussens and Werb 2002, Kanwar *et al.,* 2011*).* Table 1 summarizes the chronic inflammatory conditions associated with cancer.

Inflammatory Condition	**Associated Cancer(s)**
AIDS	Non-Hodgkin's lymphoma, squamous cellcarcinomas, Kaposi's sarcoma
Asbestosis, silicosis	Mesothelioma, lung carcinoma
Barrett's oesophagus	Oesophageal carcinoma
Bronchitis	Lung carcinoma
Chronic cholecystitis	Gall bladder cancer
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma
Coeliac disease	Lymphoma
Gingivitis	Oral squamous cell carcinoma
Helicobacter pylori infection	Gastric cancer
Hepatitis B or C	Hepatocellular carcinoma
Inflammatory bowel disease, Crohn's disease, chronic ulcerative colitis	Colorectal carcinoma
Lichen sclerosus	Vulvar squamous cell carcinoma
Mononucleosis	B-cell non-Hodgkin's lymphoma, Burkitts lymphoma,
Obesity related inflammation	Liver cancer
Opisthorchis, *Cholangitis*	Cholangiosarcoma, colon carcinoma
Osteomyelitis	Sarcoma
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma
Prostate inflammatory atrophy	Prostate cancer
Rheumatoid arthritis	Lymphoma
Shistosomiasis, bladder inflammation	Bladder carcinoma
Sialadenitis	Salivary gland carcinoma
Sjögren syndrome, Hashimoto's thyroiditis	MALT lymphoma
Skin inflammation	Melanoma

Modified from Coussens and Werb, 2002, Conro y *et al.*, 2010

Table 1. Chronic inflammatory conditions and infections associated with cancer.

When the control of cell proliferation, growth and cell death (apoptosis) is lost, we obtain a clone of cells known as benign tumour. By growing its own blood supply (angiogenesis), the tumour feeds itself, grows indefinitely and spreads (metastasizes) in the body thereby leads to malignant cancer. Tumour cells are known to produce various pro inflammatory cytokines such as IL-1β, IL-6, IL-23 and tumour necrosis factor (TNF)-αand chemokines that attract inflammatory leukocytes which include neutrophils, dendritic cells, macrophages, eosinophils, mast cells and lymphocytes (Coussens and Werb 2002, Kanwar *et al.,* 2008,). These cells further produce growth factors, various cytokines, chemokines, cytotoxic mediators like reactive oxygen species, matrix metalloproteinases (MMPs), membrane-perforating agents and soluble mediators of cell killing such as TNF-α, interleukins and interferons (Wahl *et al.,* 1998, Kuper *et al.,* 2000, Coussens and Werb 2002, Kanwar *et al.,* 2008). The recruitment of dendritic cells capture antigen and stimulate anti-tumour immunity by T lymphocyte activation which kill cancer cells via cell mediated cytotoxicity (Kanwar *et al.,* 1999). According to the immune surveillance theory, tumours arise only if cancer cells are able to escape immune surveillance, yet sometimes a robust immune response might result in a favourable effect that might be due to CD8+ cytotoxic T cells which have the capacity to kill tumour cells (Kanwar *et al.,* 2001b) CD4+ T cell responses are also important as they help recruiting CD8+ cytotoxic T cell and generate an inflammatory response that chains the function of CTLs activity (Kanwar *et al.,* 2003). The growth factors asnd cytokines released by inflammatory cells can also have pro-tumour actions. They can lead to proliferation, survival and migration of the tumour by promoting angiogenesis and lymphanogenesis, remodelling extracellular matrix to facilitate invasion, coating tumour cells to make available receptors for spreading cells via lymphatics and capillaries, and evading host mechanisms (Coussens and Werb 2002, Rigo *et al.,* 2010). In this context tumour-associated macrophages (TAMs) have a significant role. After migration the monocytes, recruited largely by monocyte chemotactic protein (MCP) chemokine become the significant component of inflammatory infiltrates as TAMs in neoplastic tissues, and has a dual role in neoplasms. TAMs may kill neoplastic cells following activation by IL-2, interferon and IL-12 or potentiate neoplastic progression through the production of a number of potent angiogenic and lymphangiogenic growth factors, cytokines and proteases, all of which are mediators for tumour growth (Brigati *et al.,* 2002, Tsung *et al.,* 2002). Further TAMs and tumour cells also produce IL-10, which effectively blunts the anti-tumour response by cytotoxic T cells, and prevent maturation of anti-tumour dendritic cells *in situ* leading to immunosuppression and immune evasion (Coffelt *et al.,* 2009). Increasing evidences have suggested that many types of cancer are closely associated with inflammation (Table 1). Thus, inflammation is a process used by immune cells to eliminate cancer and by cancer cells to promote tumour progression and metastasis.

3. CD4+ T cell subsets as essential regulators of immune responses and inflammatory diseases

Immune system consists of innate and adaptive immunity. Adaptive immunity is mediated by T and B cells. T helper cells/CD4+ cells are the key actors in establishing an immune response. Naive $CD4^+$ T cells differentiate into different types of effector cells depending upon the combination of cytokines in milieu, antigen and the antigen presenting cell (APC). There are four types known so far (Figure 1) and include T_H1, T_H2, T- regulatory (Treg) and T_H17. T_H1 cells, induced by IL-12, express T_H1 specific Transcription factors (T-bet) and

produce IFN-γ as their signature cytokine and evoke cell-mediated immunity and phagocyte-dependent inflammation. Vigorous pro-inflammatory activities of T_H1 cells has been seen to cause tissue damage and elicit unwanted T_H1-dominated responses in the pathogenesis of organ-specific autoimmune/inflammatory disorders, Crohn's disease, sarcoidosis, acute kidney allograft rejection, and some unexplained recurrent abortions (Romagnani, 2000).

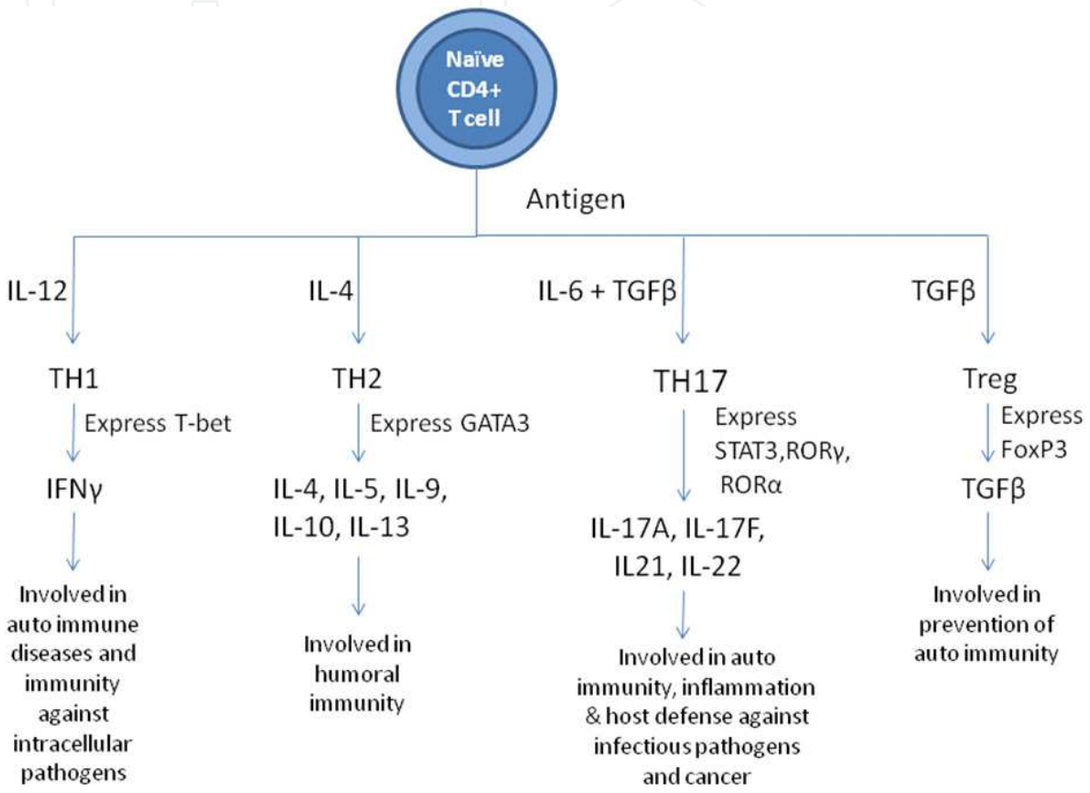

Fig. 1. CD4+ T- Cell differentiation: Naive CD4+ T cells differentiate into different effector cells under the influence of the pool of cytokines present in the surroundings. There are four known types of effector T_H cells which have different functions based on the expression of unique transcription factors and characteristic cytokines.

T_H2 cells are induced by IL-4, express GATA 3 and produce IL-4, IL-5, IL-9, IL-10 and IL-13. These are associated with the humoral immunity and resistance against extracellular forms of pathogens. T-regulatory (Treg) cells, characterized by expression of FoxP3 (forkhead/winged helix transcription factor), produce TGF-β (transforming growth factor-β1). These distinct regulatory T cell subsets suppress adaptive T cell responses, have anti-inflammatory role and are involved in maintaining tolerance to self components (prevent autoimmunity).

T_H17 cells, a newly defined lineage of CD4+ cells, are not only distinct from other T_H cells in their gene expression and regulation, but also in terms of their biological function (Dong 2008) T_H17 cells are characterized in particular through the production of IL-17 and IL-17F, and have functions in autoimmune diseases, inflammation and host defence against infectious pathogens. Recently accumulating evidence suggests that T_H cells possess

functional 'plasticity' (Bettelli *et al*., 2006, Yang *et al*., 2008a, Crome *et al*., 2010a) i.e. they can be converted into other types of T_H cells under *in vitro* as well as *in vivo* conditions. This property seems to be certainly beneficial to mount different and varied responses for combating immunological insults given at short notices.

T_H17 cells: a new lineage of effector T_H cells Discovery: The presence of T_H17 cells as a specific lineage was recognized when it was demonstrated that lipopeptides from the spirochete *Borrelia burgdorferi* triggered the increased levels of IL-17A mRNA in T cells to produce IL-17 (member of IL-17 family composed of 6 cytokines, IL-17A-F), TNF-α and GM-CSF while these cells were negative for IFN-γ or IL-4, revealing a novel cytokine phenotype distinct from T_H1 or T_H2. (Infante-Duarte *et al*., 2002). This was the first report to establish the link between bacterial infection and a new effector T cell phenotype later to become T_H17 while foretelling the description of a factor later identified as critical to T_H17 development: IL-6 (Weaver *et al.,* 2007) . Further hint came when, Aggarwal *et al*. 2003, who demonstrated that IL-23 stimulates murine CD4+ T cells to secrete IL-17 following stimulation of the T- cell receptor (TCR). These crucial findings that IL-23 but not IL-12, stimulated memory, but not naive, CD4 T cells to produce IL-17A and IL-17F, were consistent with a unique effector CD4 T cell population similar to that previously reported by Infante-Duarte and colleagues in 2002. Then the findings that IL-17 secreting CD4+ T cells arise in the absence of T_H1 and T_H2 induced transcription factors and cytokines solidified the lineage separation between T_H1/T_H2 and T_H 17 cells (Harrington *et al*., 2005; Park *et al.,* 2005).

Differentiation and transcriptional regulation: Although early studies by Aggarwal and colleagues in 2003 implicated IL-23 in driving T_H17 expression and generation , it was later on demonstrated that IL-23 receptor (IL-23R) is not expressed on naïve T cells. Instead, IL-23, as well as TNF-α, acts as survival signals for T_H17 cells. It is apparent now as reviewed recently (Weaver *et al.,* 2007, Torchinsky and Blander 2010, Kimura and Kishimoto 2011) that IL-23 is important only for T_H17 cells' expansion, survival and pathogenicity. The key cytokines required for T_H17 differentiation, surprisingly, are a combination of pro-inflammatory and anti-inflammatory cytokines; i.e, IL-6 and TGF-β respectively (Veldhoen M *et al.,* 2006, Mangan *et al.,* 2006, Betteli *et al.,* 2006). The studies by Betteli and colleagues identified TGF-β as a critical factor for T_H17 commitment while IL-6 acted to deviate TGF-β-driven development of Foxp3-expressing Tregs toward T_H17 (Betteli *et al.,* 2006).

Further attempts were made to delineate the precise signalling mechanisms through which IL-6 and TGF-β cooperate to induce T_H17 differentiation. Studies have shown that the key transcription factors in determining the differentiation of the T_H17 lineage are retinoid-related orphan receptor γt (RORγt) and RORα which can be induced by the combination of IL-6 and TGF-β (Ivanov *et al.,* 2006, Yang *et al.,* 2008b). RORγt was shown to be specifically expressed by mouse and human T_H17 cells (Ivanov *et al.,* 2006, Wilson *et al.,* 2007). Further a central role for IL-6-induced STAT3 activation was made evident. Although IL-6 activates both STAT3 and STAT1, it has been demonstrated that STAT3 activation is maintained while STAT1 activation is suppressed in T_H17 cells (Kimura *et al.,* 2007). Interferon regulatory factor (IRF) 4 and T-bet are other players in the scene of transcriptional regulation, which act as positive and negative regulators of $T_H17$commitment, respectively (Brüstle *et al., 2*007, Rangachari *et al.,* 2006). Further Aryl hydrocarbon receptor (Ahr) was shown to be induced under T_H17-polarizing conditions such as in the presence of TGF-β

plus IL-6, and promotes T_H17 cell development through inhibiting STAT1 and STAT5 activation. More recently, an AP-1 transcription factor, BATF was shown to also play a role in T_H17 differentiation. BATF-/- mice had a defect specifically in differentiation of T_H17 cells, and were resistant to autoimmune encephalomyelitis (Schraml *et al.,* 2009). IL-1 (Chung *et al.,* 2009) and IL-21 (Korn *et al.,* 2007) have also been shown to be required for their differentiation. And certain studies have shown that IL-10 released by Treg cells and IL-2 inhibit T_H17 cell development (Weaver et al., 2007). - Apart from IL-17 as its major cytokine, T_H17 cells also release IL-21 and IL-22 (Wei *et al.,* 2007, Dong 2008). As IL-21 is required for T_H17 cells' differentiation as well as is produced by them, it may be acting as a positive feedback loop to amplify the production of these cells (Torchinsky and Blander 2010). T_H17 cells also express CCR6, CXCR4, CD49 integrins and CD161 (Kryczek, *et al.*, 2009). Crome *et al.,* 2010b established a novel method to isolate *in vivo* differentiated T_H17 cells from peripheral blood by sorting CD161+CCR4+CCR6+CXCR3-CD4+T cells. These authors also suggested low expression of granzyme A and B as another distinguishing feature of T_H17 cells. T_H17 cells also express IL-23R at high levels. There exists also a negative regulatory system for T_H17 cell differentiation and IL-27 was shown to important role in curbing T_H17 responses by limiting development of T_H17 effectors (Batten *et al.,*2006, Stumhofer *et al.,* 2006). Thus, various cytokines and transcription factors can either enhance or inhibit T_H17 differentiation (Figure 2). Very recently, Martinez *et al.* in 2010 suggested that Smad2 positively regulates the generation of T_H17 cells *in vivo* and *in vitro* (Figure 3).

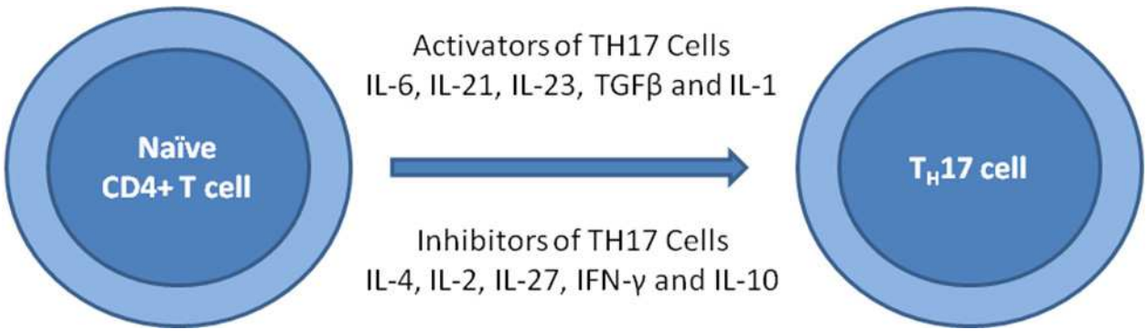

Fig. 2. Activators and inhibitors of T_H17 differentiation: The figure below shows the different activators and inhibitors which promote or inhibit the differentiation of T_H17 cells.

Cytokine production: The T_H17 lineage was originally defined by the production of hallmark cytokines interleukin-17 (also known as IL-17A) and IL-17F, members of IL-17 family (Aggarwal *et al.,* in 2003) as homodimers or heterdimers (Liang *et al.,* 2007). Later on studies have shown that $T_H17$cells are also characterized by the production of IL-10 family cytokine, IL-22 (Liang *et al.,* 2006). IL-21, besides acting in concert with TGF-β to promote T_H17 differentiation, is also produced by T_H17 cells (Korn *et al.* ,2007). T_H17 cells are also known to produce certain cytokines that are expressed by other T helper cell lineages, including TNF-α and lymphotoxin-β, and the T_H17 subset can be characterized by expression of chemokine receptor CCR6 and the CCR6 ligand, CCL20 (Hirota *et al.,* 2007, Torchinsky and Blander 2010). A subset of T_H17 cells is reported to co-expresses IFN-γ in humans where as many as half of all the IL-17+ cells also express IFN-γ. It is not yet clear if these cells represent a stable phenotype or a transitional phase, undergoing a switch from T_H17 to T_H17 or vice versa (reviewed by Tesmer *et al.,* 2008) (Figure 3).

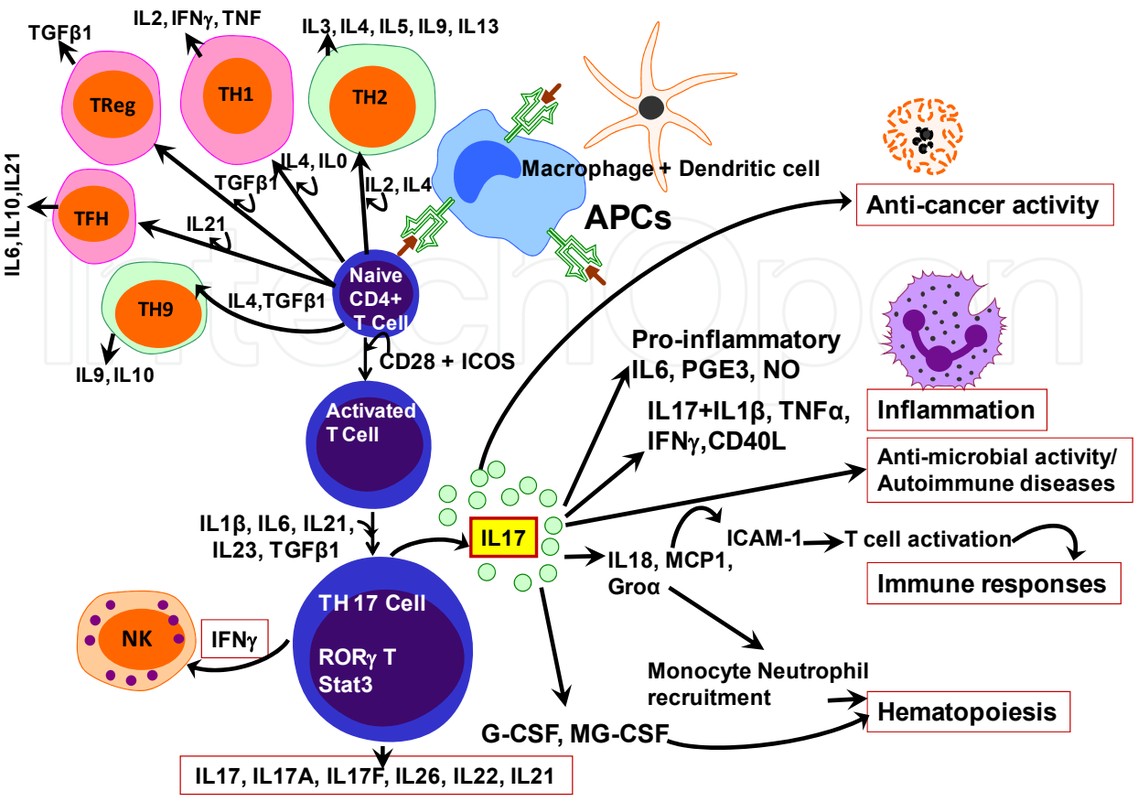

Fig. 3. T_H17 differentiation and activation of immune cells for immune responses, inflammation, anti-cancer activity and hematopoiesis.

Biological activities/functions: The important roles of IL-17 in host defence against many extracellular and intracellular pathogens have already been established (reviewed by Torchinsky and Blander 2010). IL-17A, F released by T_H17 cells, is involved in the recruitment, activation and migration of neutrophils which help the body to fight against infection with various bacterial and fungal species (Yang *et al.*, 2008c). Non-immune cells are major targets for the effector functions of T_H17 cells. Specifically, cytokines produced by T_H17 cells act on cells such as fibroblasts and keratinocytes (Chrome *et al.*, 2010) and thereby contribute to immunity in barrier tissues such as the skin and gut. T_H17 cells have also been involved with tissue repair functions through their production of the cytokine IL-22 along with IL-10 (Dong C 2008). Further the anti-infective and anti-inflammatory roles of IL-22 are associated with its functions in maintaining the integrity of epithelial barriers (Torchinsky and Blander 2010). More interestingly, it was shown that TGF-β and IL-6 from antigen presenting dendritic cells, that recognized apoptotic cells carrying TLR ligands, were able to drive differentiation of naı¨ve CD4+ T cells to the T_H17 lineage (Torchinsky *et al.*, 2009). Thus T_H17 cells may be uniquely suited to serve in host response against pathogens causing significant apoptosis and tissue damage (Figure 3).

There are effector molecules as discussed above (cytokines, chemokines and integrin α3) associated with T_H 17 cells that act as pro-inflammatory mediators of inflammation and upregulate the expression of adhesion molecules thereby mediating the migration of circulating mixed leukocytes, such as monocytes, neutrophils, T cells and natural killer (NK)

cells. The infiltrated leukocytes further augment the ongoing inflammation, indirectly by secreting an elaborated number of chemokines and cytokines, including IL-1, IL-6, TNF-α, monocyte chemoattractant protein-1(MCP-1), keratinocyte-derived chemokine (KC), IFN-γ, IL-17, and IL-23 (Coussens and Werb 2002, Kryczek *et al,* 2009a, Barreiro *et al.,* 2010),. When these inflammatory signals are altered or misprocessed, the inflammation can become chronic, causing extensive tissue damage. To combat chronic inflammation in autoimmune diseases, novel therapeutic strategies targeting T_H17 cells and their effector molecules thus represent opportunities for therapeutic intervention.

4. Association of T_H17 cells with chronic inflammation

Earlier, T_H1 phenotype was associated with inflammation and autoimmunity and now the T_H17 subset has also been described as pro-inflammatory to play a role in autoimunity and chronic inflammation. The findings that IFN-γ and IFN-γ receptor-deficient mice and mice lacking IL-12p35 and other molecules involved in T_H1 differentiation were not protected from experimental autoimmune encephalomyelitis (EAE), but rather developed more severe disease have challenged the concept that autoimmunity is a T_H1 driven disease process (Gran B *et al.,* 2002, Torchinsky and Blander 2010). The suggestion about another subset of T cells, distinct from the T_H1 lineage that might be required for the induction of EAE and other organ-specific autoimmune diseases has recently established role and importance of T_H17 cells in the pathogenesis of organ-specific autoimmune inflammation based on animal studies and clinical findings. The topic on the broad implications of T_H17 cells in the pathogenesis of number of immune-mediated diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma is beyond the scope of this chapter, but readers are referred to excellent recent reviews (Tesmer *et al.,* 2008, Dong C 2008, Torchinsky and Blander 2010, Cosmi *et al.,* 2011) (Figure 1).

Inflammation and pathogenesis induced by T_H17 cells is a result of the pro-inflammatory cytokines, chemokines and chemokine receptors these cells produce and express, respectively. Recently, T_H17 polarized cells have been shown to be associated with cancers. Cancer and inflammation are now considered to be inextricably linked. Inflammatory mediators and cellular effectors are important constituents of the local environment of tumours. Many cancers arise from the sites of infection, chronic irritation and inflammation as shown in Table 1, the inflammatory conditions are present before a malignant change occurs. To understand the kinetics and targets of inflammation in a discussion of T_H17 cells and cancer, the relationship between T_H1-derived IFNγ, T_H17 cells and antigen-presenting cells (APCs) in humans was recently studied (Kryczek *et al.,* 2008a). These authors demonstrated in a cutting edge study that IFNγ could rapidly induce elevated B7-H1 expression on APCs and stimulate their production of IL-1 and IL-23. B7-H1 signaling resulted in abrogation of the T_H1-polarizing capacity of APC, whereas IL-1 and IL-23 directed them toward a memory T_H17-expanding phenotype. These findings thus suggest that in the course of inflammation, that the acute T_H1-mediated response is attenuated by IFNγ-induced B7-H1 on APCs and is subsequently evolved toward T_H17-mediated chronic inflammation by APC derived IL-1 and IL-23. This study in addition to challenging the dogma that IFNγ suppresses T_H17 and enhances T_H1 development, also strengthens the notion that T_H17 kinetics depends strongly on the context of the ongoing immune reactions

and the constituents of the cytokine milieu, both of which are influenced by disease progression (Figure 3).

5. T_H 17 cells in cancer

Various studies have been carried out in the recent years with rapid progress on different cancer types to investigate the association of cancer and T_H17 cells. It has been seen that, T_H17 cells, might either promote tumour growth or regulate antitumour responses. This may be due to the irregular conflicting data based on the studies in humans versus those in mice and contradictory data from experiments in immunocompetent versus immunodeficient mice (Wilke *et al.,* 2011). There is, however, a strikingly high frequency of tumour-infiltrating T_H17 cells in patients with diverse cancer types. These cells when examined in cancer patients, the findings reveal that human tumour-associated T_H17 cells express minimal levels of human leukocyte antigen (HLA)-DR, CD25 and granzyme B, suggesting that they are not a 'conventional' effector cell population (Wilke *et al.,* 2011). On examining the associated mechanisms and clinical significance of T_H17 cells in 201 ovarian cancer patients, it was found that T_H17 exhibited a polyfunctional effector T-cell phenotype, were positively associated with effector cells, and were negatively associated with tumour-infiltrating Treg cells (Kryczek *et al.*, 2009a). The study authors further reveal that for homing molecules, tumour-associated T_H17 highly express chemokine receptors CXCR4 and CCR6, c-type lectin receptor CD161 and the CD49 integrin isoforms c, d and e, while CCR2, CCR5 and CCR7 are not present on these cells (Figure 3).

Several biological activities of T_H17 cells are directly or indirectly linked to human tumour pathogenesis. Tumour-associated T_H17 cells have the ability to influence the tumour immune response through the action of their cytokines products in cancer patients which reportedly include high levels of pro inflammatory granulocyte-macrophage colony stimulating factor (GM-CSF), TNF-α, IL-2 and IFNγ, but negligible levels of anti-inflammatory IL-10 . This phenotype was observed in six types of human cancers which include ovarian, colon, liver, skin, pancreatic and renal (Kryczek *et al.,* 2009a). 50% of T_H17 cells, in patients with hepatocellular carcinoma (HCC) produced IFNγ-IFNγ, a typical T_H1-type cytokine (Zhang *et al.,* 2009, Kryczek *et al.,* 2009, Wilke *et al.,* 2011). Further, on *in vitro* expansion, the $T_H17$cells from tumour-infiltrating lymphocyte populations in melanoma, breast and colon cancers secrete elevated amounts of IL-8 and TNF-α, but no IL-2 (Su *et al.,* 2010). Since this profile has been seen previously in T_H17 cells isolated from healthy donors (Liu and Rohowsky-Kochan 2008) and patients with autoimmune diseases (Kryczek *et al.,* 2008b), it may indicate a possible difference in the phenotypes of freshly isolated $T_H17$cells and those expanded or induced *in vitro* from tumour-associated populations (Figure 3). Earlier information reviewed from both experimental animal systems and human cancer patients suggested that IL-17 and IL-23 are generally favourable to the growth of tumours thus overshadowing their roles in the generation of T-cell anti-tumour immunity (Tesmer *et al.,* 2008).

Still the role of IL-17 producing T_H17 cells in cancer is elusive as different immunopathological implications of these cells have been observed in different malignancies. Analysis of tumour-derived naive and memory $CD4^+$ T cells revealed that IL-17 producing T cells are in memory phase as they are positive for CD45RO, but negative for CD45RA, CD62L, and CCR7 (Miyahara *et al.,* 2008). These authors also indicated that tumour cells may secrete key

cytokines required for the expansion of T_H17 cells. Further Su *et al.,* 2010 demonstrated elevated CD4+ T_H17 cell populations in the tumour-infiltrating lymphocytes (TILs) and suggested development of tumour-infiltrating T_H17 cells may be a general feature in cancer patients, when they extended their studies from ovarian cancers to melanoma, breast and colon cancers. Their study further demonstrated that tumour cells and tumour-derived fibroblasts, mediate the recruitment of T_H17 cells by secreting chemokines RANTES (regulated upon activation, normal T cell expressed and secreted) and MCP-1 in the tumour microenvironment. The tumour microenvironments produce a pro-inflammatory cytokine milieu and provide cell–cell contact engagement that facilitates the generation and expansion of T_H17 cells. They also showed that inflammatory TLR and nucleotide oligomerization binding domain (Nod2) 2 signalling promote the attraction and generation of T_H17 cells and that this was induced by tumour cells and tumour-derived fibroblasts.

6. Dynamic interaction between T_{reg} and T_H17 cells

Levels of both T_{reg} and T_H17 cells increase synchronically following tumour development and are inversely associated. TGF-β promotes T_{reg} development and both TGF-β plus IL-6 are required for T_H17 differentiation (Veldhoen M *et al.,* 2006, Mangan *et al.,* 2006, Betteli *et al.,* 2006). Although, both the cytokines needed for T_H17 cell development have been seen to be present in high levels in tumours (Zhou 2005), yet the levels of T_{reg} cells and other T subsets are more than T_H17 cells in both mouse and human tumours (Kryczek *et al.,* 2007). So there must be something that prevents differentiation of T_H17 cells. An interesting study by Kryczek and colleagues in 2009 from ovarian cancer patients, raised concerns on the roles of IL-6 an TGF-β, where it has been reported that inhibition of IL-1β, but not IL-6 or TGF-β, decreased T_H17 cell induction by myeloid APCs isolated from patients, and the levels of IL-17 and numbers of T_H17 cells did not correlate with the levels of IL-6 and TGF-β in these patients' samples. These observations hinted a crucial role of only IL-1β, but not of IL-6 or TGF-β, for T_H17 cell development in the ovarian cancer microenvironment. Similar support for a crucial role of IL-1β in promoting T_H17 cell development has been reported in mouse studies (Chung *et al.,* 2009, Gullen *et al.,* 2010).

According to few studies, IL-10 released by T_{reg} cells negatively regulates differentiation of T_H17 cells and IL-2, a growth factor for most T cells promote FoxP3 expression in T_H17 cells and inhibit cellular differentiation to T_H17 cells (Wilson *et al.,* 2007). Retinoic acid has been found to enhance TGF-β signalling and decrease IL-6 signalling, thus, it might also be affecting the balance between T_H17 and T_{reg} cells. Apart from this, it has also been seen that mouse peripheral mature T_{reg} can be converted to T_H17 cells favoured by inflammation and IL-6 ('plasticity') (Yang *et al.,* 2008a). The role of TGF-β in the differentiation of both induced T_{reg} cells as well as T_H17 cells, along with the documented interactions between RORα and FoxP3 that influence the two subsets, suggest a system that balances inflammation with tolerance (Figure 3).

7. Evidences for the negative and positive roles of T_H17 in anti-tumour Immunity

Though reports have addressed the presence of T_H17 cells in experimental and human tumours but they lack regarding the clear indication about either a pro-tumoural or anti-

tumoural activity of these cells (Bronte 2008).There are various biological functions of T_H17 cells and their effector molecules as mentioned earlier in the chapter that could be on the basis of experimental and clinical data, suggest T_H17 cells might either be positively or negatively co-related with cancer.

Negative role of T_H17 cells in anti-cancer

IL-17 produced by T_H17 cells is an angiogenic factor (Numasaki *et al*., 2003) which stimulates the migration and cord formation of vascular endothelial cells *in vitro* and elicits vessel formation *in vivo* which in turn promotes tumour growth and metastasis through *de novo* carcinogenesis and neovascularisation via STAT3 signalling. Another cytokine, IL-23 required for T_H17 activity has been identified as a cancer-associated cytokine because it promotes tumour incidence and growth (Langowski *et al*., 2006). It has been seen that T_H17 cells produce negligible levels of HLA- DR, CD 25, granzyme B, PD1 and FoxP3, all of which are involved in effector functions suggesting that they do not contribute to immune suppression in the tumour environment. Thus, as T_H17 cells produce pro-inflammatory cytokines and have been found to accumulate in tumour microenvironment and as inflammation is linked to cancer development and progression, it is reasonable to predict a positive relation between these cells and cancer progression. Also, the data from experiments on ovarian cancer suggest that T_H17 cells through TNF-α are involved in the development or progression of cancer in mice and humans(Charles *et al*., 2009).

Further T_H17 cells might increase their own frequency in the tumour by both direct and indirect mechanisms (Zou and Restifo 2010). The induction of T_H17 cells in the human tumour microenvironment through IL-1β production by the myeloid APCs may in turn promote dendritic cell trafficking into tumour-draining lymph nodes and the tumour environment by producing CCL20 (Kryczek *et al.,* 2009a). Further as CCR6+ T_H17 cells are known to efficiently migrate towards CCL20 (Kryczek *et al*., 2008b, Kryczek *et al*., 2009a), and CCL20 can then lead to the recruitment of dendritic cells to the tumour-draining lymph nodes and tumour itself in a CCR6-dependent manner (Martin-Orozco *et al*., 2009). Compared with corresponding non-tumour regions, the levels of T_H17 cells were found to be significantly increased in tumours of HCC patients. Most of these intratumoural T_H17 cells exhibited an effector memory phenotype with increased expression of CCR4 and CCR6. Furthermore, the intratumoural cell density of T_H17 correlated with poor survival in HCC patients (Zhang *et al*., 2009). A study from Kuang and colleagues in 2010, has demonstrated predominantly enriched levels of IL-17-producing cells in peritumoural stroma of murine HCC tissues, where their levels correlated with monocyte/macrophage density. The level of murine hepatoma-infiltrating CD4+ IL- 17+ cells as well as the tumour growth was reduced significantly when monocyte/macrophage inflammation in liver was inhibited via treatment with a Kupffer cell toxicant (gadolinium chloride).

Similar to humans, healthy mice has limited populations of T_H17 cells but these cells expanded in the blood, bone marrow and spleens but not in the tumour draining lymph nodes and largest populations were seen in tumour itself of mice with the aggressive B16 melanoma, fibrosarcoma and advanced head and neck cancers, The number of CD4+IL-17+ T cells gradually increased in the tumour microenvironment during tumour development but interestingly, the number of these cells remained limited during tumour development in the tumour draining lymph nodes, including advanced tumour stages. (Kryczek *et al*., 2007).On the other hand in nasopharyngeal carcinoma, data from human samples

demonstrated no correlation of T_H17 cells with patient clinicopathological characteristics or survival outcomes (Zhang *et al.,* 2010). Studies with patient samples from lung adenocarcinoma or squamous cell carcinoma revealed that malignant pleural effusion from these patients was chemotactic for T_H17 cells, and this activity was partially abrogated by CCL20 and/or CCL22 blockade (Ye *et al.,* 2010). Interestingly, higher infiltration of T_H17 cells in malignant pleural effusion predicted improved patient survival.

Positive role of T_H17 cells in anti-tumour immunity

Both human and mouse tumours study data suggest several lines of evidence about the protective role of T_H17 cells with the induction of protective anti-tumour immune response.T_H17 cells have been seen to positively co-relate with effector immune cells like IFNγ^+ effector T cells, cytotoxic CD8$^+$ T cells and natural killer (NK) cells in the tumour microenvironment which might be to produce an anti- tumour response against cancer cells to kill them by promoting cell mediated cytotoxicity (Kryczek *et al.,* 2009a). Various experimental studies have shown that IL-17 overexpression or exogenous T_H17 cell induction lead to decreased tumour growth, for example; Muranski and colleagues in 2008, through a first functional study showed that T_H17-polarized CD4+ T cells (following treatment with TGF-β and IL-6), induced potent tumour eradication of large established melanoma in mice. The study provides a support for a clinical trial involving the adoptive transfer of T_H17-polarized, tumour-specific CD4+ T cells to patients with cancer. A year later, another interesting functional study, revealed for the first time that T_H17-polarized CD8+ T cells induce potent tumour eradication in mice, and provided again support for a clinical trial involving the adoptive transfer of T_H17-polarized, tumour-specific CD8+ T cells to cancer patients (Hinrichs *et al.,* 2009). Once *in vivo*, T_H17-polarized CD8+ T cells might be converted to an IFNγ-producing phenotype, induced tumour regression and persisted in the host longer than non-polarized cells. tumourIL-17 deficient mice (IL-17A knockout (IL-17A -/-) have accelerated tumour growth and more lung metastasis than wild-type mice (Kryczek *et al.,* 2009b, Martin-Orozco *et al.,* 2009, Wei *et al.,* 2010). Transgenic expression of human or murine IL-17 in tumour cells suppresses or slows tumour growth and increases tumour-specific cytotoxic responses (Hirahara *et al.,* 2001, Benchetrit *et al.,* 2002). However, contrasting results were shown by Wang *et al.,* 2009 who have reported that transferred tumours of B16 and bladder carcinoma MC49 grew more slowly in IL-17-/- mice.

In prostate cancer patients, a significant inverse correlation was seen between T_H17 cell differentiation and tumour progression (Sfanos *et al.,* 2008). In addition to these evidences, it is known that IL-17 released by T_H17 cells promote dendritic cell maturation which might allow for better tumour antigen presentation and thereby leading to a stronger T cell response. Furthermore, direct mechanistic and functional evidence that T_H17 cells mediate antitumour immunity by promoting dendritic cell trafficking to tumour-draining lymph nodes, and to the tumour itself has also been provided (Martin-Orozco *et al.,* 2009). tumourtumourMore recently, CTLA4 (cytotoxic T lymphocyte antigen 4) blockade was shown to increase T_H17 cells in patients with metastatic melanoma and IL-17 levels in tumour-associated ascites positively predicted patient survival (von Euw *et al., 2009).* To summarize the above data, there is strong evidence that T_H17 cells can have protective roles in tumour immunity but the exact nature of T_H17 cells in anti-tumour immunity remains to be explored.

8. Conclusions

Rapid and large advances in understanding the development, regulation and function of these cells have been made since T_H17 cells are originally identified as a third lineage of effector T helper cells in 2005. The study of T_H17 cells has been one of the fast-moving and exciting subject areas in immunology. This has been particularly true in the context of a diverse group of immune-mediated chronic inflammatory diseases and autoimmunity, where the pathogenic role of T_H17 cells has been well documented. With regards to cancer, T_H17 cells are found to be present in the tumour microenvironment though not as a predominant T cell subset within the tumour. Based on the evidence provided by both human and clinical studies data, T_H17 cells and T_H17-associated cytokines/effector molecules have been shown to have both pro-tumorigenic and anti-tumorigenic functions. On one hand it seems that the pro-inflammatory T_H17 cells might engineer the microenvironment around tumours, and contribute to the proliferation, migration and survival of cancer cells. On the other hand, it is possible that inflammatory cells and molecules play roles to initiate and maintain protective anti-tumour immunity as seen in the case of infectious diseases (Punj *et al*., 2003). The IL-17 dependent pro-tumorigenic or anti-tumorigenic activity might be due to inherent technical limitations for example source and dose of exogenous versus endogenous IL‑17, in each of the studies (Zou and Restifo 2010). Further, based on the results from recent murine model studies, employing T_H17-polarized T cells for cancer therapy may appear to be to be a promising approach for translational research. It is also important to study futher the specific nature of inflammatory response and the tissue context, so that the positive or negative effects of T_H17 cells on tumour immunopathology can be determined. Equally important to understand is i) how the effector functions of $T_H17$cells are regulated?, ii) how do the regulators of T_H17-cell differentiation work? iii), do T_H17 play same role in different types and stages of cancer?, and iv) how T_{reg} cells can be suppressed in chronic inflammatory or large tumour burdens to increase the T_H17 cells and later activation and proliferation of cytotoxic T cells to clear tumour cells? The answers will, help in designing future novel therapeutic vaccine approaches; specifically targeting inflammatory T_H17 cells for cancer therapy.

9. Abbreviations

CD	Cluster of Differentiation
IL	Interleukin
IFN	Interferon
TNF	Tumour Necrosis Factor
TGF	Tumour Growth Factor
MMP	Matrix Metalloproteinase
APC	Antigen Presenting Cells
FoxP3	Forkhead Box P3
MAPK	Mitogen-Activated Protein Kinases
TRAF6	Tumour Necrosis Factor Receptor-Associated Factor-6
TLR	Toll-like Receptors

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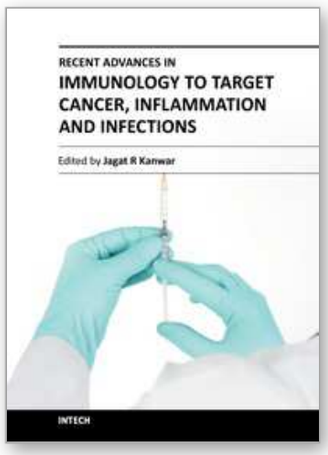

Recent Advances in Immunology to Target Cancer, Inflammation and Infections

Edited by Dr. Jagat Kanwar

ISBN 978-953-51-0592-3
Hard cover, 520 pages
Publisher InTech
Published online 09, May, 2012
Published in print edition May, 2012

Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Rupinder K. Kanwar and Jagat R. Kanwar (2012). TH17 Cells in Cancer Related Inflammation, Recent Advances in Immunology to Target Cancer, Inflammation and Infections, Dr. Jagat Kanwar (Ed.), ISBN: 978-953-51-0592-3, InTech, Available from: http://www.intechopen.com/books/recent-advances-in-immunology-to-target-cancer-inflammation-and-infections/th17-cells-in-cancer-related-inflammation

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