1. Introduction

Until 2005, T helper (CD4+) cells were proposed to be a binary system, consisting of Th1 and Th2 cells (Mosmann TR et al., 1986). When a third T helper -cell subset, known as Th17 (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 Th17 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 Th17 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 Th17 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 Th17 cells, their role as friends or foes, respectively is still under debate; could be because of a few studies have focused on primary Th17 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 Th17 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.

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

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)-α and 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 and 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 lymphangogenesis, 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 Th1, Th2, Th- regulatory (Treg) and Th17. Th1 cells, induced by IL-12, express Th1 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\(_H\)17 cells: a new lineage of effector T\(_H\) cells**

**Discovery:** The presence of T\(_H\)17 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-\(\alpha\) and GM-CSF while these cells were negative for IFN-\(\gamma\) or IL-4, revealing a novel cytokine phenotype distinct from T\(_H\)1 or T\(_H\)2. (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\(_H\)17 while foretelling the description of a factor later identified as critical to T\(_H\)17 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 naïve, 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\(_H\)1 and T\(_H\)2 induced transcription factors and cytokines solidified the lineage separation between T\(_H\)1/T\(_H\)2 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\(_H\)17 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-\(\alpha\), acts as survival signals for T\(_H\)17 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\(_H\)17 cells’ expansion, survival and pathogenicity. The key cytokines required for T\(_H\)17 differentiation, surprisingly, are a combination of pro-inflammatory and anti-inflammatory cytokines; i.e, IL-6 and TGF-\(\beta\) respectively (Veldhoen M et al., 2006, Mangan et al., 2006, Betteli et al., 2006). The studies by Betteli and colleagues identified TGF-\(\beta\) as a critical factor for T\(_H\)17 commitment while IL-6 acted to deviate TGF-\(\beta\)-driven development of Foxp3-expressing Tregs toward T\(_H\)17 (Betteli et al., 2006).

Further attempts were made to delineate the precise signalling mechanisms through which IL-6 and TGF-\(\beta\) cooperate to induce T\(_H\)17 differentiation. Studies have shown that the key transcription factors in determining the differentiation of the T\(_H\)17 lineage are retinoid-related orphan receptor \(\gamma\)t (ROR\(\gamma\)t) and ROR\(\alpha\) which can be induced by the combination of IL-6 and TGF-\(\beta\) (Ivanov et al., 2006, Yang et al., 2008b). ROR\(\gamma\)t was shown to be specifically expressed by mouse and human T\(_H\)17 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\(_H\)17 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\(_H\)17 commitment, respectively (Brüstle et al., 2007, Rangachari et al., 2006). Further Aryl hydrocarbon receptor (Ahr) was shown to be induced under T\(_H\)17-polarizing conditions such as in the presence of TGF-\(\beta\).
plus IL-6, and promotes T\textsubscript{H}17 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\textsubscript{H}17 differentiation. BATF-/- mice had a defect specifically in differentiation of T\textsubscript{H}17 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\textsubscript{H}17 cell development (Weaver et al., 2007). - Apart from IL-17 as its major cytokine, T\textsubscript{H}17 cells also release IL-21 and IL-22 (Wei et al., 2007, Dong 2008). As IL-21 is required for T\textsubscript{H}17 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\textsubscript{H}17 cells also express CCR6, CXCR4, CD49 integrins and CD161 (Kryczek, et al., 2009). Crome et al., 2010b established a novel method to isolate \textit{in vivo} differentiated T\textsubscript{H}17 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\textsubscript{H}17 cells. T\textsubscript{H}17 cells also express IL-23R at high levels. There exists also a negative regulatory system for T\textsubscript{H}17 cell differentiation and IL-27 was shown to important role in curbing T\textsubscript{H}17 responses by limiting development of T\textsubscript{H}17 effectors (Batten et al.,2006, Stumhofer et al., 2006). Thus, various cytokines and transcription factors can either enhance or inhibit T\textsubscript{H}17 differentiation (Figure 2). Very recently, Martinez et al. in 2010 suggested that Smad2 positively regulates the generation of T\textsubscript{H}17 cells \textit{in vivo} and \textit{in vitro} (Figure 3).

**Fig. 2. Activators and inhibitors of T\textsubscript{H}17 differentiation:** The figure below shows the different activators and inhibitors which promote or inhibit the differentiation of T\textsubscript{H}17 cells.

**Cytokine production:** The T\textsubscript{H}17 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\textsubscript{H}17 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\textsubscript{H}17 differentiation, is also produced by T\textsubscript{H}17 cells (Korn et al., 2007). T\textsubscript{H}17 cells are also known to produce certain cytokines that are expressed by other T helper cell lineages, including TNF-α and lymphotixin-β, and the T\textsubscript{H}17 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\textsubscript{H}17 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\textsubscript{H}17 to T\textsubscript{H}17 or vice versa (reviewed by Tesmer et al., 2008) (Figure 3).
TH17 Cells in Cancer Related Inflammation

Fig. 3. TH17 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 TH17 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 TH17 cells. Specifically, cytokines produced by TH17 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. TH17 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 naive CD4+ T cells to the TH17 lineage (Torchinsky et al., 2009). Thus TH17 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 TH17 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 TH17 cells and their effector molecules thus represent opportunities for therapeutic intervention.

4. Association of TH17 cells with chronic inflammation

Earlier, TH1 phenotype was associated with inflammation and autoimmunity and now the TH17 subset has also been described as pro-inflammatory to play a role in autoimmunity and chronic inflammation. The findings that IFN-γ and IFN-γ receptor-deficient mice and mice lacking IL-12p35 and other molecules involved in TH1 differentiation were not protected from experimental autoimmune encephalomyelitis (EAE), but rather developed more severe disease have challenged the concept that autoimmunity is a TH1 driven disease process (Gran B et al., 2002, Torchinsky and Blander 2010). The suggestion about another subset of T cells, distinct from the TH1 lineage that might be required for the induction of EAE and other organ-specific autoimmune diseases has recently established role and importance of TH17 cells in the pathogenesis of organ-specific autoimmune inflammation based on animal studies and clinical findings. The topic on the broad implications of TH17 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 TH17 cells is a result of the pro-inflammatory cytokines, chemokines and chemokine receptors these cells produce and express, respectively. Recently, TH17 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 TH17 cells and cancer, the relationship between TH1-derived IFNγ, TH17 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 TH1-polarizing capacity of APC, whereas IL-1 and IL-23 directed them toward a memory TH17-expanding phenotype. These findings thus suggest that in the course of inflammation, that the acute TH1-mediated response is attenuated by IFNγ-induced B7-H1 on APCs and is subsequently evolved toward TH17-mediated chronic inflammation by APC derived IL-1 and IL-23. This study in addition to challenging the dogma that IFNγ suppresses TH17 and enhances TH1 development, also strengthens the notion that TH17 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. TH17 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 TH17 cells. It has been seen that, TH17 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 TH17 cells in patients with diverse cancer types. These cells examined in cancer patients, the findings reveal that human tumour-associated TH17 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 TH17 cells in 201 ovarian cancer patients, it was found that TH17 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 TH17 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 TH17 cells are directly or indirectly linked to human tumour pathogenesis. Tumour-associated TH17 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 TH17 cells, in patients with hepatocellular carcinoma (HCC) produced IFNγ-IFNγ, a typical TH1-type cytokine (Zhang et al., 2009, Kryczek et al., 2009, Wilke et al., 2011). Further, on in vitro expansion, the TH17cells 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 TH17 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 TH17 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 TH17 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<sub>H</sub>17 cells. Further Su et al., 2010 demonstrated elevated CD4<sup>+</sup> T<sub>H</sub>17 cell populations in the tumour-infiltrating lymphocytes (TILs) and suggested development of tumour-infiltrating T<sub>H</sub>17 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<sub>H</sub>17 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<sub>H</sub>17 cells. They also showed that inflammatory TLR and nucleotide oligomerization binding domain (Nod2) 2 signalling promote the attraction and generation of T<sub>H</sub>17 cells and that this was induced by tumour cells and tumour-derived fibroblasts.

6. Dynamic interaction between T<sub>reg</sub> and T<sub>H</sub>17 cells

Levels of both T<sub>reg</sub> and T<sub>H</sub>17 cells increase synchronically following tumour development and are inversely associated. TGF-β promotes T<sub>reg</sub> development and both TGF-β plus IL-6 are required for T<sub>H</sub>17 differentiation (Veldhoen M et al., 2006, Mangan et al., 2006, Betteli et al., 2006). Although, both the cytokines needed for T<sub>H</sub>17 cell development have been seen to be present in high levels in tumours (Zhou 2005), yet the levels of T<sub>reg</sub> cells and other T subsets are more than T<sub>H</sub>17 cells in both mouse and human tumours (Kryczek et al., 2007). So there must be something that prevents differentiation of T<sub>H</sub>17 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<sub>H</sub>17 cell induction by myeloid APCs isolated from patients, and the levels of IL-17 and numbers of T<sub>H</sub>17 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<sub>H</sub>17 cell development in the ovarian cancer microenvironment. Similar support for a crucial role of IL-1β in promoting T<sub>H</sub>17 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<sub>reg</sub> cells negatively regulates differentiation of T<sub>H</sub>17 cells and IL-2, a growth factor for most T cells promote FoxP3 expression in T<sub>H</sub>17 cells and inhibit cellular differentiation to T<sub>H</sub>17 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<sub>H</sub>17 and T<sub>reg</sub> cells. Apart from this, it has also been seen that mouse peripheral mature T<sub>reg</sub> can be converted to T<sub>H</sub>17 cells favoured by inflammation and IL-6 (‘plasticity’) (Yang et al., 2008a). The role of TGF-β in the differentiation of both induced T<sub>reg</sub> cells as well as T<sub>H</sub>17 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<sub>H</sub>17 in anti-tumour Immunity

Though reports have addressed the presence of T<sub>H</sub>17 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 TH17 cells and their effector molecules as mentioned earlier in the chapter that could be on the basis of experimental and clinical data, suggest TH17 cells might either be positively or negatively co-related with cancer.

**Negative role of TH17 cells in anti-cancer**

IL-17 produced by TH17 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 TH17 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 TH17 cells produce negligible levels of HLA-DR, CD25, 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 TH17 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 TH17 cells through TNF-α are involved in the development or progression of cancer in mice and humans (Charles et al., 2009).

Further TH17 cells might increase their own frequency in the tumour by both direct and indirect mechanisms (Zou and Restifo 2010). The induction of TH17 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+ TH17 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 TH17 cells were found to be significantly increased in tumours of HCC patients. Most of these intratumoural TH17 cells exhibited an effector memory phenotype with increased expression of CCR4 and CCR6. Furthermore, the intratumoural cell density of TH17 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 TH17 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 TH17 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 TH17 cells, and this activity was partially abrogated by CCL20 and/or CCL22 blockade (Ye et al., 2010). Interestingly, higher infiltration of TH17 cells in malignant pleural effusion predicted improved patient survival.

**Positive role of TH17 cells in anti-tumour immunity**

Both human and mouse tumours study data suggest several lines of evidence about the protective role of TH17 cells with the induction of protective anti-tumour immune response. TH17 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 TH17 cell induction lead to decreased tumour growth, for example; Muranski and colleagues in 2008, through a first functional study showed that TH17-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 TH17-polarized, tumour-specific CD4+ T cells to patients with cancer. A year later, another interesting functional study, revealed for the first time that TH17-polarized CD8+ T cells induce potent tumour eradication in mice, and provided again support for a clinical trial involving the adoptive transfer of TH17-polarized, tumour-specific CD8+ T cells to cancer patients (Hinrichs et al., 2009). Once in vivo, TH17-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. Tumour IL-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 TH17 cell differentiation and tumour progression (Sfanos et al., 2008). In addition to these evidences, it is known that IL-17 released by TH17 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 TH17 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). Tumour tumour tumour tumour tumour...
8. Conclusions

Rapid and large advances in understanding the development, regulation and function of these cells have been made since TH17 cells are originally identified as a third lineage of effector T helper cells in 2005. The study of TH17 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 TH17 cells has been well documented. With regards to cancer, TH17 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, TH17 cells and TH17-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 TH17 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 TH17-polarized T cells for cancer therapy may appear to be to be a promising approach for translational research. It is also important to study further the specific nature of inflammatory response and the tissue context, so that the positive or negative effects of TH17 cells on tumour immunopathology can be determined. Equally important to understand is i) how the effector functions of TH17 cells are regulated?, ii) how do the regulators of TH17-cell differentiation work? iii), do TH17 play same role in different types and stages of cancer?, and iv) how Treg cells can be suppressed in chronic inflammatory or large tumour burdens to increase the TH17 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 TH17 cells for cancer therapy.

9. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CD</td>
<td>Cluster of Differentiation</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
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<tr>
<td>TGF</td>
<td>Tumour Growth Factor</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix Metalloproteinase</td>
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<tr>
<td>APC</td>
<td>Antigen Presenting Cells</td>
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<tr>
<td>FoxP3</td>
<td>Forkhead Box P3</td>
</tr>
<tr>
<td>MAPK</td>
<td>Mitogen-Activated Protein Kinases</td>
</tr>
<tr>
<td>TRAF6</td>
<td>Tumour Necrosis Factor Receptor-Associated Factor-6</td>
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<tr>
<td>TLR</td>
<td>Toll-like Receptors</td>
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10. References


TH17 Cells in Cancer Related Inflammation


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Recent Advances in Immunology to Target Cancer, Inflammation and Infections


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.

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