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Review Article

Biology of TH17 Cells and Their Role in Inflammatory Diseases

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T lymphocytes that are involved in cellular mediated immunity include two types known as TCD8+ (cytotoxic T lymphocytes) and TCD4+ (helper T lymphocytes). TCD4+ has four main subtypes, including TH1, TH2, TH17, and Treg lymphocytes. TH17 lymphocytes play a role in defense against microbes while TH1 and TH2 lymphocytes have not the ability to respond to them. The most important cytokines which are involved in the induction of this subtype are the tumor growth factor β (TGF-β) and interleukin 6 (IL-6). IL-17 is the most important cytokine released by TH17 cells. IL-17 is the member of a cytokine family which include IL-17A-F, among which IL-17A and IL-17F show more homology together compared to the other members, and are responsible for biological functions. Also, TH17 cells produce and release other cytokines such as IL-21, IL-22 and IL-23, which may have a role in the functional mechanisms of TH17 lymphocytes. Because of TH17 lymphocytes roles in the defense against microbes and inflammatory reactions, it seems that they may have a role in inflammatory disorders. The relationship between TH17 lymphocytes and diseases such as asthma, psoriasis, systemic lupus erythematosus, rheumatoid arthritis and inflammatory bowel disease was shown. In this article, we review the TH17 lymphocytes, their released cytokines and their roles in different autoimmune and inflammatory diseases.

Keywords: TH17 lymphocytes, cytokine, inflammatory diseases

T-cells, which play the most important role in cell-mediated immunity, include two subgroups of $TCD8^+$ (CTL) and $TCD4^+$ (TH) cells. TH cells were divided into TH1 and TH2 cells in mid-1980. TH1 are mainly differentiated from TH0 cells by the expression of IFN-γ, IL-12 as well as STAT1 and STAT4 transcription factors. TH2 cells also are differentiated from TH0 by the expression of IL-4 as well as STAT6 and GATA3 transcription factors and produce IL-3, IL-5 and IL13 [1, 2]. TH17 cells are the third group of TH cells, which were identified for the first time in 2005. They are primarily active against microbes including extracellular bacteria and fungi upon which TH1 and

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TH2 cells are not effective (1-3). TH17 cells are defined by the expression of RORγC transcription factor, IL-23 R, chemokine receptor CCR6, as well as lectin receptor CD161 (4). IL-17 is the most important cytokine produced by these cells, and TGF-β is involved in their differentiation and induction. Low-dose of TGF-β together with IL-6 causes differentiation of TH0 towards TH17 lymphocytes, but induces FOXP3 expression and differentiation to Treg lymphocytes in high dose (5). IL-6, IL-1 and IL-21 could also play a role in differentiation of TH17 cells as well as TGF-β (6). (Figure 1) shows different subtypes of helper T lymphocytes, their cytokines and mechanism of action.

The most important cytokines produced by Th17 lymphocytes

Interleukine 17 (IL-17)

IL-17 was first isolated as a cDNA transcript called CTLA8 from activated hybrid T- cells in rodents (7). IL-17 is different from other cytokines. It also differs from other proteins in terms of structure and domain. IL-17 receptor has 860 amino acids and has no similarity to any cytokine receptor or detectable protein domains (8). Several genes including IL-17 A-F encoding this cytokine family have been characterized (9). This cytokine is released by activated $CD4^+$ and $CD8^+$ memory cells, with both TH1 and TH2 subsets secreting it. IL-17

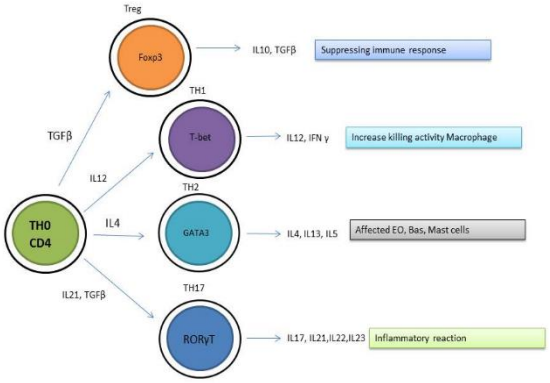


Figure 1. Subtypes of helper T lymphocytes, their cytokines and mechanism of action.

receptor is expressed on almost all body cells, including lung and epithelial cells (10). TCR α/β, $CD4^-$ and $CD8^-$ cells are the only source of this cytokine in mouse (11). IL-17A was discovered in 1993 as the first member of IL-17 family (7). It was first named cytotoxic T-lymphocyte-associated serine esterase-8 consisting of a prototype member of IL-17 cytokine family composed of 155 amino acids with a homodimer of 30-35 KDa molecular weight (12). IL-17A gene is located on chromosome 6p12 and presents 62% homology with mouse Il-17A gene (13). Initially, IL-17A was thought to increase inflammation through the induction of neutrophil and macrophage chemokines as well as growth factors such as CXCL1, CXCL2, CXCL18, CXCL5, G-CSF and GM-CSF (14). It also increase the production of antimicrobial peptides such as serum amyloid A and C reactive proteins (15). IL-17F is another member of IL-17 cytokine family with the highest level of homology with IL-17A. IL-17F gene is located at the same locus as IL-17A but binds IL-17R with lower affinity and less biological activity (16). IL-17A and IL-17F exist as both IL17A/IL17A and IL17F/IL17F homodimers as well as IL17F/IL17A heterodimer, among which IL17A/IL17A can induce proinflammatory cytokines with higher effectiveness (17). Other members of IL-17 family include IL-17B, IL17C, IL-17D and IL-17E, which unlike IL-17A and IL-17F, are produced by sources other than T-cells. IL-17RA is widely expressed on epithelial cells, fibroblasts, macrophages, dendritic cells, vascular endothelial cells and peripheral blood T-cells. IL-17RC is mainly expressed in prostate, cartilage, kidney, liver, heart and muscle cells (18-20). IL-17R is a type I trans-membrane protein with 293 amino acids in the extracellular domain, 21 amino acids in trans-membrane domain and 525 amino acids in cytoplasmic tail, which is mainly expressed in lung, kidney, liver and spleen cells as well as fibroblasts,

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Table 1. Characteristics of IL-17 cytokine family

IL-17 subtype	Size (KDa)	Length (number of aa)	Chromosomal location	Produced mainly by	Binding receptor
A	35	155	6p12	T cells	IL-17RA, IL-17RC (IL-17RL)
B	41	180	5q32-34	Numerous tissues	IL-17RB
C	40	197	16q24	Prostate, fetal kidney	
D	52	202	13q12.11	Numerous tissues	
E	34	161	14q11.2	Numerous tissues	IL-17RB (IL-25R)
F	44	153	6p12	T cells	IL-17RA, IL-17RC

epithelial and myeloid cells of rats and mice (21). (Table 1) shows some characteristics of members of IL-17 cytokine family.

IL-17 signaling

IL-17A receptor does not show homology with other receptors, and so uses a signal transduction pathway different from other receptors. In this receptor, similar to the above-mentioned receptors, nuclear factor NF-κB which is a typical transcription factor in inflammation, is activated (21). The SEFIR domain in ACT1 is a signaling adaptor associated with NF-kB activity via BAFF (B-cell activating factor) and CD40L, and defects in ACT1 disrupt the function of NF-κB induced by IL-17A and IL-17F. Unlike IL-17A receptor, there is TRAF-6 binding motif in ACT1, which can bind TRAF6, TRAF3 and TAK1 (22). MAPKs are other factors that play an important role in the activity of inflammatory cytokines, and eventually activate AP-1 trans-cription factor. IL-17A receptor activates several MAP kinases; however, compared to other MAPKs, ERK has a prominent role in this regard due to higher phosphorylation rate. In general, the main role of MAP kinases in regulating the expression of IL-17 is mediated by increasing the stability of mRNA through inhibition of destabilizing proteins, including tristetraprolin (TTP). These proteins bind AU rich regions in mRNA transcripts and direct them towards exosome complex for degradation. Phosphorylation of these regions via MAP kinases blocks their ability to degrade mRNA, causing increased mRNA survival (23). (Figure 2) shows the signal transduction pathways of IL17 cytokine family.

Interleukine 21 (IL-21)

IL-21 is a member of a cytokine family with common gamma chain, including IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 (24). The most important cells producing these cytokines include $TCD4^+$ and NKT cells. TH17 and TFH lymphocytes are the most important IL-21 producing $TCD4^+$ cells, and IL-21 receptor is expressed in B and T lymphocytes as well as NK cells, macrophages and dendritic cells (25). IL-21 has different functions, and its association with inflammatory bowel disease, ulcerative colitis,

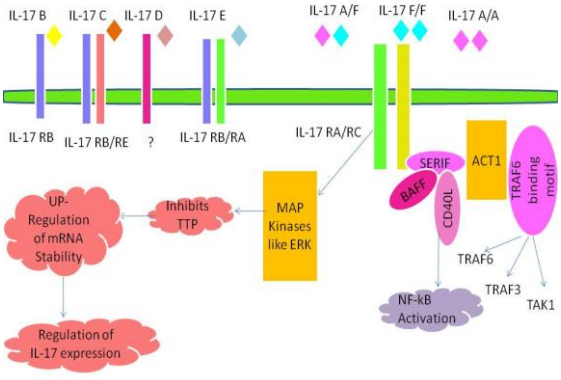


Figure 2. Signal transduction pathway of IL-17 cytokine family.

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Table 2 Cytokine produced by TH17 lymphocytes and diseases associated with their deficiency

Diseases associated with Th17 deficiency	Transcription factors	Cell surface Receptors	Cytokines produced by Th17 lymphocytes
SLE	RORγt	IL-6R	**IL-17A**
RA	STAT-3	TGF-BRII	**IL-17F**
Athma	STAT-4	IL-23R	**IL-21**
IBD	----	TCR	**IL-22**
-------	----	CD4	**IL-23**
-------	----	CCR4	**TNF-α**
-------	----	CCR6	**IFN-γ**

systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and asthma has been indicated (26-28). In combination with TGFβ, this cytokine induces IL-17 production in naive $CD4^+$ T-cells and can increase TH17 cells. In fact, IL-21 produced by TH17 cells induces the expression of RORγT, IL-17A, and IL-17F, and therefore acts as an autocrine regulator (29). IL-21 also affects other immune cells. In early B-cells, it increases anti-CD40 mediated proliferation, IL-15 and FLT3L mediated proliferation of NK cells, as well as antigen and anti-CD3 dependent proliferation of T cells (24).

Interleukine 22 (IL-22)

IL-22 is another cytokine produced by Th17 cells. IL-22 was first described as an inducible IL-10 associated factor derived from T cells (30) and belonging to IL-10 cytokine family, including IL-22, IL-10, IL-19, IL-20, IL-24, IL-26, IL-28, and IL-29 (31). This cytokine is mainly released by T-cells, especially $TCD4^+$ cells. Memory cells produce a higher level of IL-22 compared to activated naive cells and TH1 cells produce more IL-22 than TH2 and TH17 cells do (32-34). It has a heterodimer receptor, which consists of IL-10β and IL-22R chains primarily expressed on non-hematopoietic cells such as epithelial cells of the respiratory and digestive systems, as well as skin keratinocytes (35).

TH17 lymphocytes and inflammatory diseases

Inflammation is the protective response against the injuries which its classical signs include pain**,** swelling, redness, heat and malfunction. Inflammatory disorder can result in humans in disease involving the allergic reaction or immune system disorders as well as some myopathies. After discovering TH17 cells, its role have been studied in several diseases such as RA, SLE, inflammatory bowel disease and psoriasis (36). (Table 2) shows different cytokines produced by TH17 lymphocytes and diseases associated with their deficiency.

Systemic lupus erythematosus and rheumatoid arthritis

SLE is a systemic autoimmune disease caused by complement activation and immune complex deposition in the vascular tissue. TH cells, including TH1 and TH2, can play a role in the pathogenesis of this disease via cytokines production (37, 38). After introduction of TH17 cells, it was found that this subgroup of T-cells is involved in production of inflammatory cytokines such as IL-17, IL-21 and IL-22, and studies were undertaken to assess its association with SLE (39). IL-17 produced by these cells can play a role in SLE pathogenesis via increa-

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sed production of IgG against dsDNA (40), as well as an increase in spontaneous formation of germinal centers (41). In addition, in patients with SLE, serum level of IL-17 has been shown to be much higher than that of normal subjects, with increased TH17 cell response compared with healthy individuals (42). The expression of TH17 related genes is increased in urine sediment of patients with SLE and is decreased with reduced disease activity (43), which could be due to systemic inflammation and increased activation of T-cells or can indicate the facilitation of the pathway leading to IL-17 production by T-cells in patients with SLE (44).

Although several cytokines can be involved in the pathogenesis of RA, studies show that IL-17 plays a major role in tissue damage, and its binding to IL-17R can increase inflammation and joint damage through the induction of matrix metalloproteinases (MMPs) and osteoclasts as well as inhibition of proteoglycan synthesis (45). Therefore, the use of antibodies against IL-17 can reduce bone and cartilage destruction and can also inhibit the formation of osteoclasts (46). In several studies, increased IL-17 level has been shown in synovial fluid of patients with RA. IL-15 appears to stimulate IL-17 production and cause increased production of IL-1 and TNF (47). IL-17 can induce the expression of IL-6 as well as IL-1, and along with them can play a role in joint damage *in vitro* and *in vivo* (48).

Asthma

Many studies have indicated a link between asthma and TH17 cells (49, 50). As previously stated, IL-17 is a main cytokine of TH17 cells, and its increased level can thus represent an increase in TH17 lymphocytes. In patients with asthma, TH17 measurement in sputum samples of patients can be helpful in determination of prognosis and indicates severity of disease, with higher levels in patients suffering from severe asthma than in patients with mild and moderate asthma (50). Moreover, IL-17 has other cell sources, and its secretion by eosinophils has been reported, which can result in increased synthesis of IL-6 and IL-11, leading to an increase in bronchial fibroblast cells (51). Studies have reported the secretion of IL-17 by lung macrophages in response to mast cell mediators (52) as well as TH2 cells (53). In fact, TH2 cells are a subset of TH cells that synthesize and release inflammatory TH17 cytokines, like IL-17 and IL-22 in addition to producing TH2 specific cytokines, such as IL-4 and IL-13, expressing TH17 associated RORγT and TH2 associated GATA3 transcription factors (53).

Psoriasis

Psoriasis is an inflammatory skin disease caused by infiltration of T-cells and other immune cells to the skin. TH17 cells and cytokines produced by them are important immune factors involved in psoriasis (54-56) . TH17 and $Foxp3^+$ regulatory T cells (Tregs) are increased in peripheral blood and skin lesions of patients with psoriasis in proportion to the severity of disease, and Treg suppression effect on TH17 is reduced in these patients (54). There is an increased level of IL-17 as well as lymphocytes secreting IL-17 in skin lesions of patients with psoriasis compared with healthy individuals (55-57). As mentioned earlier, IL-22 and IL-23 are cytokines involved in biology of TH17 cells, and their role in psoriasis has also been shown (58-61). IL-22 is involved in the regulation of gene products implicated in psoriasis. In fact, it increases the expression of these genes in proportion to increase in IL-22 level, which is higher in blood of patients with psoriasis relative to healthy controls. Studies have shown the increasing expression of IL-22 in the skin plaques. Also, its circulating level is related with severity of disease. Furthermore, it can increase the expression of some genes which have role in the psoriasis disease (62).

IL-23 is increased in patients with psoriasis,

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which may lead to an increase in IL-17A and IL-17F, causing mobilization of neutrophils as well as increasing TNF levels (63). Also, studies have been shown that TH17 cells and Treg cells FOXP3$^+$ are reduced in the both blood circulation and skin lesions of the patients with psoriasis (54). In addition, increasing expression of IL-17 cytokine is showed in the biopsy of the skin lesions.

Inflammatory bowel disease

Crohn's disease and ulcerative colitis are two important chronic recurrent inflammatory bowel diseases in human, characterized by chronic inflammation of tissue altering the function and integrity of the intestine. Various factors can contribute to the development of these diseases; in fact, they are caused by the interaction between environmental and genetic factors. The role of immune cells in these diseases has been indicated. It was first believed that TH1 cells are important in the inflammation and thay are TCD4$^+$ cells that can produce proinflammatory cytokines when they have been activated in response to intestinal microbial flora (64). However, various studies have shown that TCD4$^+$ cells, especially the subgroup producing IL-17, are the most important immune cells involved in the disease (65). Moreover, the role of inflammatory cytokines such as IL-1β, IL-12, IL-8 and IFNγ as well as IL-17 has been shown in production of this cytokine (66-68). Hence, increased production of inflammatory cytokines subsequent to increased TH cells can lead to increased risk of the disease. It was shown that IL-17 level is specifically higher in patients with inflammatory bowel disease, which was highly increased in patients with active Crohn's disease than in patients with ulcerative colitis (69). In addition, TH17 and Treg Foxp3$^+$ cells are increased and decreased in patients with inflammatory bowel disease, respectively, which is likely to reduce its suppressive function (70).

Conclusions

Discovery of the TH17 lymphocytes and their function in the immunity result in understanding of their role in the pathophysiology of most of autoimmune and inflammatory diseases. Although the functional mechanism is not clear well, it seems that the cytokines released from these cells have a key role in these diseases. IL-17 is the most important cytokine, which is released by TH17 cells and its increased serum level have been shown in these diseases, therefore it seems that this cytokine may have a central role, although other cytokines such as IL-21, IL-22 and IL-23 may also play a role in pathogenesis of the diseases.

Conflict of interest

The authors declared no conflict of interests.

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