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Association of TH17 cell and IL-17A With Autoimmune Inflammatory Disorders: A Review

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Abstract
T helper17 cells consider as essential pathogenic T cell subset in some pathological situations that associated with T helper1 cells. The pathology of autoimmune diseases are related with these cells and also these cells important in the clearance of extracellular infections. Interleukin17A is the major cytokine that produced from T helper 17 cells. These cells in addition to Treg cells are differentiated from naive T cells and can be controlled by cytokine milieu, such as Treg cells induction need for transforming growth factor β, whereas the same cytokine stimulates the T helper 17 populations to differentiate under effect of interleukin 6 or interleukin1. Furthermore, the T helper 17 can be maintenance by interleukin 23. The massive information about T helper 17 is fundamental for recognition of its etiological participation and for evolution of therapeutic approach that related with combat T helper 17 related diseases. In this review, we effort to highlight on the importance of these cells and their cytokines in expansion of autoimmune diseases in human.

Keywords: Autoimmune disease, T helper 17 cells, Interleukin 17A.

Introduction

T helper17 are a class of CD4 T lymphocytes, specified in immunity against some extracellular bacteria and fungi **(1).** The most cytokine produced by T helper 17 is interleukin-17A **(2)**, also cytotoxic T lymphocytes, and innate lymphocytes cells such as natural killer T cells can produced this cytokine **(3).**

The role of immune system in the body is to remove the different invaded infectious microorganisms and cancerous cells that result from different types of mutations. Under some circumstances the immune system reaction leads to cell death. Therefore, in chronic inflammatory disorders the excessive excluded of targets is deleterious and is behind development of autoimmune disorders. Thus, accurate regulation is essential to keep immunological balance. CD4 subset lymphocytes are called helper T cells because it is responsible for regulation of immune cells function. These helper cells are play a crucial role in the removal of different infections. In addition, these cells produce different cytokines which stimulate efficient immune response by immune cells. Interleukin 17 participate in immunity against both extracellular and intracellular organisms **(4, 5. 6).** Also, this cytokine has important function in the pathogenesis of different autoimmune disorders. T helper 17 lymphocytes are responsible for production of other interleukines in addition to interleukin 17A, such as interleukins 17F, 21, 22 and 26 in human which responsible for immune defense against pathogens **(7)**.

Indeed, some diseases like mucocutaneous candidiasis is associated with genetic disturbance in the cytokine pathway of T helper 17 lymphocytes **(8).**

ROR γt (retinoic acid receptor related orphan receptor γt) and transcription factor expression are responsible for antigen recognition by natural killer T cells, γδT cells and innate cells **(3).**

The causes of autoimmune diseases are associated with dysregulation of protective immune response. The onset of autoimmune disease risk increased when disturbance occur in the equilibrium between regulatory and self-reactive lymphocytes. Increased interleukin 17 production is accompanied with high T helper 17 generation and this may lead to autoimmune diseases. Although interleukin 17 can produce by several types of cells, cumulative data has highlighted T helper lymphocytes major role in autoimmunity process **(9).**

Overview about T helper 17 cells:

CD4+ T helper lymphocytes play important role in the immune cells activation like cytotoxic T cells and B cells and consider as a mediator of cellular immunity, also have a critical role in the regulation of immune response. These cells are divided into subsets and recognized by effector function and cytokine production, in response to signal from innate immune cells, CD4 Th lymphocytes can differentiated in the periphery. Th1 and Th2 are the first two of these subsets, and this classification present for several years before discover of a new subpopulation of CD4 T helper cells, named T helper17 that responsible for production of interleukin 17A **(10).**

T helper 17 cells can be differentiated from naïve $CD4^+$ T cells in the periphery similar to other T helper cells subsets in response to T cell receptor antigen stimulation and promoting antigen presenting cells for production of cytokines. Whilst T helper cells differentiation was induced by interleukin 23, it was subsequent found that cells development located independently of this cytokine. However,as yet thought that interleukin 23 to be crucial for proliferation and survival of T helper 17 cells, and interleukin 23 receptor is related with activation of these cells. The combination of TGFβ, interleukin-6 and interleukin-21 are crucial for differentiation of T helper17 cells. Both interleukins 6 and 21 are responsible of drive expression of T helper 17 transcriptional regulators through STAT3 signaling, committing $CD4^+$ T cells to the T helper 17 lineage. Decreased the expression of

interleukin 23 receptor, key T helper 17 associated transcription factors, and effector cytokines such as interleukins 17A and 17F were associated with defects in this signaling pathway. RORyt is responsible for differentiation of T helper 17. Both interleukin 17A and 17F expression can be induced by this transcription factor and deficiency of this factor may lead to reduced T helper 17 function and development **(11).**

Final studies recognized a related transcription facter RORα similar to RORyt which can also drive the differentiation and cytokine expression of T helper 17 cells in response to STAT3. The deficiencies of both RORα and RORyt factors lead to inhibition of T helper 17 development because both these factors act synergistically to promote commitment of T helper 17 **(12).**

IRF4, BATF, and AHR represent the other transcription factors that associated with development of T helper 17 lymphocytes. The exact function of IRF4 in biology of T helper 17 is not fully identified, but it is thought to be upstream of RORyt, as the capability of naïve $CD4^+$ T cells to upregulate RORyt expression is reduced in its absence **(13).** A nuclear factor AHR shared with T regulatory cells but in T helper 17 subset expressed at higher concentrations. Whilst the deficiency of this factor dose not influence the differentiation of T helper 17 subset but secretion of effector cytokines, specially interleukin 22 is significantly diminished **(14).**

Finally, BATF factor has been demonstrated to be fundamental for generation of T helper 17 cells and cytokines expression, in spite of the perception that transcription factor is not alone to the T helper 17 lymphocytes lineage and that factor deficient cells are yet as able for stimulating RORα and RORyt **(15).**

T helper 17 cells and cytokine agents

The T helper 17 lineage can be recognized by interleukin 17 secretion **(16),** a member of interleukin 17 cytokines family. Another study showed that these cells are also identified by secretion of other cytokine in this family which is called interleukin 17F and interleukin 22 of interleukin 10 family cytokine **(17).**

These T helpers 17 subpopulation are able to secret a specific cytokine which expressed by another T helper subset, such as lymphotoxin-β & tumor necrosis factor-α. These cells express receptor for chemokine like CCR6, CCR6 ligand and CCL20 **(18).**

Both interleukins 17A and IL-17F have 50 % of amino acid identity and secreted by T helper 17 lymphocytes **(19).** Whilst, these interleukins are related to inflammatory condition, the accurate functions of various secreted cytokines types are still to be clarified.

In addition, The interleukin 22 secreted by T helper 17 after differentiation of naive CD4 T cells toward the T helper 17 subtype, also during T helper 17 cells restimulation in an interleukin 23 dependent mode **(17).**

Also, Interleukin 10 that belongs to interleukin 10 family is expressed by several T helper 17 subsets but not all. This cytokine is an anti-inflammatory cytokine that assists to control of mediated inflammatory process by T helper 1 and T helper 17 cells **(20).**

Host defense by TH17 cells:

Kolls and his colleagues were the first researchers whom study the effect of IL-17 on defense against microbial infections, the study was done on_IL-17 receptor deficient mice and reveal the dissemination of Klebsiella pneumoniae in lung with increase number of bacteria in spleen and increase mortality rate after infection through intranasal rout **(21)**.

Delayed recruitment of neutrophil together with defective expression of colony stimulating factor (G-CSF) and CXCL-1 were the factors responsible for enhancement of this infection **(22)**. For those IL-17R-deficient mice exogenous G-CSF administration does not restore the level of neutrophil in lung tissue and this is due to the fact that those mice have defective CXC chemokines production in addition to defective G-CSF production **(23).**

IL-17 response is upregulated by IL-23 in infection with the same pathogen and IL-23p19-deficient mice again are highly susceptible to K. pneumoniae infection. In addition, administration of recombinant IL-17 for IL-23p19-deficient mice resulted in decrease number of bacteria and effective chemokine responses **(24).** Susceptibility for K. pneumoniae infection is demonstrated in IL-17A-deficient mice also with reduction of G-CSF and CXC chemokines levels **(25).** Collectively these studies clarify the significant role of IL-23p19 and IL-17 in protection against K. pneumoniae infection through effective recruitment of neutrophil in pulmonary tissues.

IL-17 and Autoimmune Diseases:

Autoimmune disorders have different etiological background and unclear pathogenesis. Defects in central and peripheral tolerance is one of etiological factors that lead to emergence of autoreactive lymphocytes (both T & B cells). Expansion of these lymphocytes occur after exposure to self-antigens and result in abnormal immune response. There are two types of autoimmune diseases: organ specific and systemic autoimmune diseases. Inflammation and tissue damage will follow the abnormal immune response **(26).** Many studies highlighted the function of IL-17 in autoimmunity as increase expression in both human and animal models. Role of IL-17 in autoimmunity pathogenesis is explained within this section.

1. Rheumatoid arthritis (RA):

Infiltration of CD4+ lymphocytes together with increase synovial fibroblasts, plasm cells producing autoantibodies and joint destruction are the whole criteria of RA. IFNγ and TNFα and_other Th1cytokines were hypothesized to be the cause of autoimmunity as they present within synovial tissues and peripheral blood **(27).**

IL-17 and its corresponding receptor were found to be increases joints of RA patients compared to control and osteoarthritic patients as declared by past studies **(28).** In addition, IL-17 was regarded as bad prognostic factor in RA patients **(29).** Neutrophil recruitment and chemokines secretion occurred under the effect of IL-17 leading to joint erosion **(28).** IL-17 is a proinflammatory cytokine that activate different cells as synovial fibroblast and other inflammatory cells (monocytes & macrophages) leading to production of inflammatory cytokines (like TNFα, IL-1β, IL-6, chemokines and growth factors) with consequence destructive picture that seen in RA **(30).**

2. Systemic Lupus Erythematosus (SLE):

In SLE there are autoantibodies produced against self-antigens forming immune complexes that deposit in different sites as blood vessels of skin, kidneys and joints leading to inflammation and damage which aggravate the autoimmune process **(31).**

IL-17 acting as proinflammatory cytokine is partly responsible for autoimmune response in SLE, a study showed that DN T-cells expansion and producing IL-17 result in tissue inflammation in lupus nephritis **(32).** The exact role for IL-17 is unclear but indirect increment of autoantibodies producing cells is possible through enhancement of B-cell survival **(33).**

3. Psoriasis:

Psoriasis is a chronic autoimmune disease of skin associated with cells infiltrate within tissue. It was thought that psoriasis is Th1induced disease, but later on focusing on Th17 cell role in disease development was the concern of various researchers. Biopsies from inflamed lesions reveal increase expression IL-17 mRNA **(34).** Disease activity is directly associated with IL-17 levels. Local detection of Th17 cells in inflamed lesions together with Th1 cells **(35).**

Synergistic effect of IL-17, IFNγ, TNFα and IL-22 enhance cytokine and chemokines secretion which augment inflammation in psoriasis. IL-17 plus IFNγ lead to IL-8, IL-6 and ICAM-1 (intracellular adhesion molecule-1) secretion within keratinocytes. IL-17 plus TNFα augment genes of inflammation in psoriasis. Lastly, IL-17 plus IL-22 lead to antimicrobial peptides expression in skin as S100A8/9 (calprotectin), β-defensin-2 (BD-2) & S100A7 (psoriasin) **(26).**

Treatment by T helper 17 cells:

Targeting TH17 cells in treatment of inflammatory and autoimmune diseases is based on the role of these cells and their cytokines in pathogenesis of these diseases, psoriasis treatment by antibodies against IL-12p40 (called IL-12β) is more common nowadays in addition to antibodies targeting IL-17A. This treatment type for rheumatoid arthritis is less likely but it is more effective in multiple sclerosis where the active lesions decreases by IL-17-specific antibody administration **(36).**

IL-23 has important role in pathology of spondyloarthropathies, as psoriatic arthritis and ankylosing spondylitis through action on innate cells at entheses producing IL-17 and IL-22 **(37).** Although treatment by IL-23 antibodies are not yet applicable and IL-17 antibodies therapy does not have much effect on spondyloarthropathies **(36).**

Keeping in mind that when treating inflammatory diseases by targeting TH17 cells the inherent plasticity for these cells could change target and may lead to production of IFNγ and/or GM-CSF with turning off IL-17 secretion. The side effects for this type of treatment constitute a major obstacle for this approach as when treating psoriasis mucocutaneous *C. albicans* infection could arise because of IL-17 defensive role against opportunistic infections. In case of Crohn's disease, the treatment could be harmful in some patients **(38).** For these cases clearance of *C. albicans*_infections was difficult due to defective IL-17 pathway **(39).**

The side effects of cytokines targeting in TH17 cell pathway are serious condition more than targeting TH17 cells as RORγt-dependent IL-17-secreting cells (γδ T cell and ILC3s) with inhibition of transcription factors like RORγt. Inhibition of TH17 cell differentiation was proofed in previous study by compounds that antagonized RORγt transcriptional effects, although TH17 in small intestine is not assessed **(40).**

Reduction of TH17 population in mice with intestinal inflammation by inhibition of RORγt either by genetic or pharmacological ways was suggested bt another study without affecting ILC3s number that express RORγt also, although TH17 in small intestine was not assessed again **(41).**

Similar results with suppression of TH17 population (by blocking deacetylation of RORγt) through inhibition of protein deacetylase sirtuin 1 with pharmacological method was reported in another study **(42).**

Another emerging problem in TH17 cells targeting therapeutic approach is the possibility of developing tumors as T cell lymphomas **(43).** So, careful evaluation for TH17 cells targeting therapeutic approach is required with counterbalance of their potential side effects.

Conclusions

Interleukin-17A and T-helper17 are distinguished as a marker that associated with clearance of different types of pathogens and also related with various autoimmune disorders.

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