IL-17 and IL-17R: an auspicious therapeutic target for psoriatic disease

A. Mitra$^{a,c}$, S.K. Raychaudhuri$^{a,b}$ and S.P. Raychaudhuri$^{a,b,*}$

$^a$VA Medical Center Sacramento, Mather, CA, USA
$^b$University of California, Davis, School of Medicine, Internal Medicine/Rheumatology, Allergy & Clinical Immunology, Davis, CA, USA
$^c$University of California, Davis, Dermatology, School of Medicine, Sacramento, CA, USA

Abstract The continuous discovery of new T cell subpopulations in human autoimmune diseases is making the immunopathological network more complex. Th17 cells are one such newly identified subset of T cells, characterized by the production of signature cytokine IL-17. In last few years, several studies have strongly established the regulatory role of Th17 cells and its signature cytokine IL-17 in autoimmune diseases including psoriasis, psoriatic arthritis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus and multiple sclerosis. Psoriasis and PsA are immune mediated hyperproliferative diseases, affecting skin and joint respectively. Before the discovery of Th17 cells, psoriasis and psoriatic diseases were thought to be chiefly Th1 mediated diseases; later on IL-17 knockout animal studies as well as human experimental data indicate the crucial role of Th17 cells and its signature cytokine IL-17 in the pathogenesis of these diseases. In vitro human studies have shown the abundance of Th17 cells in the psoriatic plaques. Subsequently our research group has extended this observation in psoriatic arthritis and found the abundance of CD4+IL-17+ T cells in the synovial fluid and majority of these T cells are of memory phenotype (CD4RO+CD45RA-CD11a+). In addition, we showed the significant presence of functional IL-17 receptor in synovial fibroblast of psoriatic arthritis patients. Considering the strong association of IL-17 and psoriatic disease, IL-17 targeted therapy have shown promises in preclinical and clinical trials. In this review article, we have discussed the pathogenic role of IL-17 in psoriatic disease and summarized the therapeutic efficacy and safety profile of different anti IL-17 therapy as an anti-psoriatic agent.

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*Corresponding author.
E-mail address: srAYchaudhuri@ucdavis.edu (S.P. Raychaudhuri).

IL-17 e IL-17R: una diana terapéutica favorable para la enfermedad psoriásica

Resumen El descubrimiento continuo de nuevas subpoblaciones de células T en las enfermedades autoinmunes humanas está haciendo el sistema inmunopatológico más complejo. Las células Th17 son uno de los subgrupos de células T nuevamente identificados, caracterizados por la producción de citocina IL-17. En los últimos años, muchos estudios han establecido fuertemente el papel regulador de las células Th17 y su distintiva

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citocina IL-17 en enfermedades autoinmunes como psoriasis, artritis psoriásica, artritis reumatoide, enfermedad intestinal inflamatoria, lupus eritematoso sistémico y esclerosis múltiple. La psoriasis y la artritis psoriásica son enfermedades hiperproliferativas mediadas inmunológicamente, que afectan la piel y la articulación, respectivamente. Antes del descubrimiento de las células Th17, se pensaba que la psoriasis y las enfermedades psoriásicas eran enfermedades mediadas principalmente por Th1; más tarde, el impacto de los estudios en animales sobre la IL-17, así como los datos experimentales en humanos, indican el papel crucial de las células Th17 y su distintiva citocina en la patogénesis de estas enfermedades. Los estudios humanos in vitro han mostrado la abundancia de células Th17 en las placas psoriásicas. Posteriormente, nuestro grupo de investigación ha prolongado esta observación en la artritis psoriásica y ha encontrado abundancia de CD4+ IL-17+ células T en el líquido sinovial; la mayoría de estas células T son de fenotipo de memoria (CD4RO+CD45RA-CD11a+). Además, hemos demostrado la presencia significativa del receptor funcional de IL-17 en los fibroblastos sinoviales de los pacientes con artritis psoriásica. Teniendo en cuenta la potente asociación de la Il-17 y la enfermedad psoriásica, la terapia enfocada en la IL-17 ha mostrado ser prometedora en estudios preclínicos y clínicos. En este artículo de revisión hemos analizado el papel patogénico de la IL-17 en la enfermedad psoriásica y hemos resumido la eficacia terapéutica y el perfil de seguridad de una terapia anti IL-17 diferente como agente antipsoriásico.

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Introduction

Psoriasis and psoriatic arthritis (PsA), often termed as ‘psoriatic disease’ are autoimmune diseases of skin and joint respectively. In last few years, although substantial progress has been made in understanding the pathogenesis of psoriatic disease, but still exact cause remains a mystery. Psoriatic disease is considered as multifactorial in nature; a combination of genetic, immunologic and environmental factors contribute to its pathogenesis by modulating the function of lymphocytes, neutrophils, epidermal keratinocytes and relevant cytokines. Psoriatic disease imparts a huge socioeconomic burden including almost annual direct and indirect cost of US$11 billion. Psoriatic arthritis (PsA) is a seronegative immunologically triggered chronic inflammatory joint disease; develops in ~25% of the psoriasis patients usually within 10 years after the onset of skin manifestations. In ~10% of PsA patients, the arthritis appears before the onset of skin disease. Apart from PsA, psoriasis is associated with multiple comorbidities such as hypertension, dyslipidaemia, diabetes mellitus, obesity, non-alcoholic fatty liver disease and metabolic syndrome. In addition, it is also associated with psychological comorbidities including anxiety, depression and suicidal tendency.

Genetics in psoriasis

Psoriatic disease has a strong genetic component as evidenced by family and twin studies, linkage studies and population based association studies. Several studies have identified a number of susceptibility loci for psoriatic disease in the innate immunity (NFκB and IFN) signaling pathway (TNFAIP3, TNIP1, NFKBIA, REL, TYK2, IFI1, IL23RA) and β-defensin, adaptive immunity involving CD8 T cells (ERAP1, ZAP70) and Th17 pathway (IL12B, IL23A, IL23R, TRAF3IP2, TYK2), Th2 pathway (IL4, IL13) and the skin barrier proteins (LCE3B, LCE3C). These observations suggest the significance of both keratinocytes and the immune cells in the pathophysiology of psoriasis. In addition, association between apolipoprotein E variants (Apo e4) and psoriasis indicates the crosstalk of lipid metabolism and psoriasis. In PsA, it has been shown that HLA-B22 plays a protective role in disease progression; whereas HLA-B27 is associated with spinal involvement, and HLA-B38/HLA-B39 is associated with peripheral joint involvement. Further genetic studies in psoriatic arthritis reported a less severe course of joint disease with both HLA-Cw6 and HLA-DRB1*07 than patients with HLA-C26 or HLA-DRB1*07 alone. Immunopathogenesis of psoriatic disease

The immunopathogenesis of psoriatic disease is complex and still evolving. In this complex milieu, pathogenic T cell subpopulations (Th1, Th17, Th22) and their signature cytokines (IFN-γ, IL-1β, IL-6, TNFα, IL-17, IL-22), chemokines, adhesion molecules, growth factors like nerve growth factor (NGF) and neuropeptides act in an integrated way through their corresponding receptors to evolve pathognomonic features of psoriasis. In last few years, extensive scientific effort has been put to understand the immunological network of psoriatic disease. Discovery of new cytokines and chemokines contributes to better understanding of the disease pathogenesis, but still the hierarchy of these agents need to be established. The role of innate and adaptive immune responses are now well established in its pathogenesis. Psoriatic disease is strongly believed as a T cell mediated autoimmune disease of the skin and synovial fibroblast based upon the following observations: a) CD4+ T cells targeted immunotherapy clears active plaques of psoriasis; b) transplanted nonlesional psoriatic skin converts to a psoriatic plaque subsequent to intradermal

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administration of T cells activated with an antigen cocktail in SCID mice; c) blocking of the T cell co-stimulatory molecule improves psoriasis in the SCID mouse-psoriasis xenograft model; d) IL-22, a relatively new proinflammatory cytokine contributes to pannus formation in PsA.20-23

Till 1970s, psoriasis was believed to be a primary disorder of keratinocyte proliferation/differentiation, and inflammatory infiltrates were considered as secondary phenomenon.4,24 Later on, strong evidences regarding the role of inflammatory infiltrates made the clinician and scientists believe that it is a T cell mediated skin disease, and regarded as Th1 mediated disease due to presence of IFN-γ and IL-12.4,25,26 With time, new subset of T cells and associated cytokines have been shown to play an important role in psoriatic disease: Th17 and IL-17,23,27,32 Th22 and IL-22,23,31-33 IL-23,30 IL-21,36 IL-27,37 IL-9.18 In addition to these new cytokines, tumour necrosis factor-α (TNFα) and interleukin 12 (IL-12) are well established immunological mediators in psoriatic disease.2,4,32,39 The role of Th17 and Th22 cytokines in psoriatic disease are substantiated by the significant presence of IL-17A, IL-17F, IL-22, and TNFα (both Th1 and Th17 cytokine) in serum, synovial fluid and skin lesions of these patients.13,27,31,40-45 Several in vitro and ex vivo studies showed the increased expression of the Th17 specific transcription factor-RORγt, and the cytokines required for differentiation of Th17 cells such as IL-23, IL-6 and IL-1β in psoriatic milieu, validating the crucial role of Th17 and its signature cytokine IL-17 in psoriatic disease at molecular level.45,51 These observations are confirmed by in vivo mouse studies.29,46,52,53 Genome wide association studies also suggest the significance of IL-23/Th17 pathway in psoriasis.27,28 These findings suggest that not only TNFα, but IL-23/IL-17 also plays a central role in psoriatic disease and thus is expected that blocking of TNF by anti-TNF agents may not be adequate for treatment of psoriatic disease. This makes IL-17 and its receptor (IL-17R) a sizzling therapeutic target for psoriasis and other autoimmune diseases. Herein, we will summarize the pathogenic role of IL-17/IL-17R in psoriatic disease, the therapeutic efficacy and safety concerns of IL-17 targeted therapy.

**T cell subpopulations**

Before going into the role of IL-17 in psoriatic disease, we will recapitulate the differentiation of naïve T cells into pathogenic subset of T cells. In 1986, Mosmann and Coffman proposed the existence of Th1 and Th2 phenotype based on their cytokine profile: Th1 cells chiefly produce pro-inflammatory cytokines- IFN-γ, IL-2, whereas Th2 cells produce anti-inflammatory cytokines- IL-3, IL-10.34 Psoriasis was considered as Th1 disease due to abundance of Th1 cytokines in the psoriatic milieu.4,35 In late 2005, this paradigm of Th1/Th2 was challenged with the discovery of a distinct subset of T cells chiefly producing interleukin-17 (IL-17), which was termed as Th17 cells.33,56 Though Th17 cells were discovered in 2005, but its signature cytokine, IL-17 is known for much longer period of time, since mid 90s.4,73 The differentiation of naïve T cells to effector lineages is governed by the local cytokine milieu.58 Naïve T cells differentiate to Th1 cells and Th2 cells in presence of IL-12 and IL-4 respectively. The specific transcription factor for Th1 and Th2 cells are T-bet and GATA-3 respectively.58,59 Inspite of enormous progression in understanding the Th17 differentiation, still there are some controversies regarding the cytokine milieu which induces differentiation of Th17 cells from naïve T cells. This might be attributed to several factors including the difference in Th17 cytokine biology in mouse and human, presence of TGF-β in the serum used for tissue culture media.56 The majority consensus is that in presence of TGF-β, IL-23, IL-1β and IL-6, naïve T cells differentiate into Th17 cells.58,60,61 In the complex cytokine milieu, Th1 and Th2 cells suppresses each other and also inhibits Th17 differentiation, in contrast Th17 cells do not have inhibitory effect on Th1/Th2 cells.51,55,58 The survival and expansion of Th17 cells are dependent on IL-23 and IL-21.26,62,64

**Chemokine receptors of pathogenic Th17 cells**

For migration of activated pathogenic T cells to the local disease site, chemokines and chemokine receptors plays a crucial role. Inspite of some sharing of chemokine receptors in between different subsets of T cells, each T cell subset have specific chemokine receptor(s), which helps in migration of the respective T cell subsets in the local disease site. Th17 cells express the CC chemokine receptor, CCR6 and CCR4.65,66 Further it was confirmed by showing that most of the RORγt (transcription factor for Th17 cells) expressing cells are CCR6+ and CCR4+.66 Interestingly, Th17 cells also expresses the ligand for CCR6, CCL20 (macrophage inflammatory protein 3, MIP-3A). IL-17 induces release of CCL20 from the stromal cells, thus favours the recruitment of more and more Th17 cells in the local disease site, resulting in disease progression.58,65,67,68

**IL-17 and its receptor**

In early 90s, the IL-17 encoding gene was discovered in a rodent T cell library,24 followed by identification of its human homologue with a cytokine like activity, and termed as IL-17.55 Simultaneously, the receptor for IL-17 was characterized and found to be unrelated to previously identified cytokine receptor families.24,25 IL-17 is considered as the signature cytokine of Th17 cells, and the encoding gene is proximally located on chromosome 6.58 Till date, six cytokines in the family of IL-17 has been discovered, named IL-17A through IL-17F. IL-17A (commonly termed as IL-17) is the widely studied Th17 cytokine followed by IL-17F. IL-17A and IL-17F has 55% amino acid similarity and exists as homodimers.69,70 In addition to homodimers, few evidences suggest the existence of a heterodimer, IL-17A/F with inflammatory potential.71,72 IL-17A and IL-17F homodimers shares structural similarity, have di-sulfide bond and a cysteine-knot fold.73,74 Akin to IL-17 cytokine, IL-17 receptor (IL-17R) complex is multimeric too. The first discovered subunit of IL-17R complex is IL-17RA; later on other subunits of this complex have been identified and termed as IL-17RB, IL-17RC, IL-17RD and IL-17RE.75-78 IL-17A and IL-17F binds to the receptor complex formed by IL-17RA and IL-17RC resulting in activation of intracellular signalling
Facilitate the effect of TNF-α to IL-17 heightens much more compared to IL-17 alone. In the presence of other pro-inflammatory cytokines, the effect of IL-17 is expressed ubiquitously and its expression is upregulated in autoimmune diseases. IL-17 contributes to both acute and chronic stages of inflammation. IL-17 induces release of IL-6, IL-8 and G-CSF from epithelial cells and mesenchymal cells, which contributes to acute phase responses like fever (through IL-6), expansion of neutrophilic lineage (through G-CSF) and accumulation of neutrophils (through chemokines, IL-8). Apart from its effect on innate immune cells (neutrophils), IL-17 exerts its effect on crucial local effector cells and contributes significantly in the disease pathogenesis. Further, the role of IL-23/IL-17 in psoriasis was substantiated in IL-17-/- mice studies. In autoimmune arthritis, IL-17 induces hyperproliferation of synovial fibroblasts resulting in pathognomonic ‘pannus’ formation. It induces the release of antipapoptotic protein ‘synoviolin’ from the synovial fibroblasts, thus favours the survival of these key effector cells and perpetuate the chronicity. IL-17 also induces release of pro-inflammatory cytokines and chemokines form the synovial fibroblasts and thus perpetuates the local inflammatory milieu in autoimmune arthritis. It has an inhibitory effect on tissue matrix production by inducing the function of matrix metalloproteinases and also contributes in osteoclastogenesis, resulting in irreversible cartilage damage in autoimmune arthritis. It has been shown to have a role in development of germinal centers and production of autoantibodies. In the complex in vivo cytokine milieu, in presence of other pro-inflammatory cytokines, the effect of IL-17 heightens much more compared to IL-17 alone. IL-17 facilitates the effect of TNF-α by inducing the expression of TNFR2, and TNF-α stabilizes the IL-17 mRNA, resulting in synergistic effect. As IL-17 and TNF-α shares few terminal effector responses, patients not responding to anti TNF therapy can be tried with IL-17/IL-17R targeted therapy. IL-17 acts like a double edged sword. In autoimmune diseases, IL-17 aggravates the disease progression and chronicity, in contrast it plays a protective role in bacterial and fungal infection. IL-17 exerts its protective effect in gram positive and negative bacterial infection by recruiting neutrophils and inducing several antimicrobial genes. Similarly, IL-17 and its receptor plays a protective role in fungal infections, and one recent human study showed chronic mucocutaneous candidiasis in patients with IL-17RA and IL-17F deficiency, further proves the crucial role of this class of cytokine and its receptor in mucosal immunity. Thus, IL-17 exerts a strong protective role against extracellular pathogens. In contrast to TNF-α, the role of IL-17 against intracellular pathogens such as Mycobacterium tuberculosis and Listeria monocytogenes is less crucial. Therefore, drug targeting IL-17/IL-17R pathway has less potential to induce infections with intracellular pathogens compared to the TNF pathway.

Functional role of IL-17

The two most well studied cytokine of IL-17 family, IL-17A and IL-17F contributes significantly in the tissue inflammation. Among the IL-17 family, IL-17A is the most potent inflammatory cytokine followed by IL-17A/IL-17F heterodimer and IL-17F. Herein, we will discuss briefly the functional role of IL-17 cytokines. IL-17R is expressed ubiquitously and its expression is upregulated in autoimmune diseases. IL-17 contributes in both acute and chronic stages of inflammation. IL-17 induces release of IL-6, IL-8 and G-CSF from epithelial cells and mesenchymal cells, which contributes to acute phase responses like fever (through IL-6), expansion of neutrophilic lineage (through G-CSF) and accumulation of neutrophils (through chemokines, IL-8). Apart from its effect on innate immune cells (neutrophils), IL-17 exerts an effect on crucial local effector cells and contributes significantly in the disease pathogenesis. Further, the role of IL-23/IL-17 in psoriasis was substantiated in IL-17-/- mice studies. In autoimmune arthritis, IL-17 induces hyperproliferation of synovial fibroblasts resulting in pathognomonic ‘pannus’ formation. IL-17 induces release of antipapoptotic protein ‘synoviolin’ from the synovial fibroblasts, thus favours the survival of these key effector cells and perpetuates the chronicity. IL-17 also induces release of pro-inflammatory cytokines and chemokines form the synovial fibroblasts and thus perpetuates the local inflammatory milieu in autoimmune arthritis. It has an inhibitory effect on tissue matrix production by inducing the function of matrix metalloproteinases and also contributes in osteoclastogenesis, resulting in irreversible cartilage damage in autoimmune arthritis. It has been shown to have a role in development of germinal centers and production of autoantibodies. In the complex in vivo cytokine milieu, in presence of other pro-inflammatory cytokines, the effect of IL-17 heightens much more compared to IL-17 alone. IL-17 facilitates the effect of TNF-α by inducing the expression of TNFR2, and TNF-α stabilizes the IL-17 mRNA, resulting in synergistic effect. As IL-17 and TNF-α shares few terminal effector responses, patients not responding to anti TNF therapy can be tried with IL-17/IL-17R targeted therapy. IL-17 acts like a double edged sword. In autoimmune diseases, IL-17 aggravates the disease progression and chronicity, in contrast it plays a protective role in bacterial and fungal infection. IL-17 exerts its protective effect in gram positive and negative bacterial infection by recruiting neutrophils and inducing several antimicrobial genes. Similarly, IL-17 and its receptor plays a protective role in fungal infections, and one recent human study showed chronic mucocutaneous candidiasis in patients with IL-17RA and IL-17F deficiency, further proves the crucial role of this class of cytokine and its receptor in mucosal immunity. Thus, IL-17 exerts a strong protective role against extracellular pathogens. In contrast to TNF-α, the role of IL-17 against intracellular pathogens such as Mycobacterium tuberculosis and Listeria monocytogenes is less crucial. Therefore, drug targeting IL-17/IL-17R pathway has less potential to induce infections with intracellular pathogens compared to the TNF pathway.

Role of IL-17 in psoriatic disease

With the discovery of a new subset of pathogenic pro-inflammatory T cells, Th17 cells, several studies have shown the regulatory role of Th17 and its signature cytokine, IL-17 in autoimmune diseases including rheumatoid arthritis, psoriasis, psoriatic arthritis, crohn’s disease, ankylosing spondylitis, multiple sclerosis. Among the human autoimmune diseases, the relevance of IL-17 and its receptor system have come initially from studies in rheumatoid arthritis. Later on the regulatory role of IL-17 is well substantiated in psoriatic disease. Lesional psoriatic skin showed upregulated expression of IL-17 family cytokines (IL-17A, IL-17C and IL-17F) compared to non-lesional psoriatic skin, and the expression of IL-17A showed positive correlation with disease severity. Studies by our research group and other have shown abundance of IL-17A+ T cells in the skin and synovial tissue of patients with psoriasis and psoriatic arthritis respectively. Further, overexpression of the Th17 specific transcription factor (ROrγt) and Th17 inducing cytokines (IL-23, IL-6, IL-1β) in lesional psoriatic skin compared to nonlesional skin and skin of healthy volunteers substantiated the relevance of IL-17 in the pathogenesis of psoriasis. Initially, due to overexpression of p40 subunit of IL-12 in psoriatic skin, it was thought to be a Th1 mediated disease, as IL-12 induces differentiation of Th1 cells. Later on, it was found that p40 is a shared subunit of IL-12 and IL-23. Thus, the interpretation of psoriasis as a Th1 disease was redone based on further evidences. To confirm the Th1/Th17 polarity of psoriasis, focused studies have done and found that psoriatic lesions are enriched with p40 subunit (shared by IL-12 and IL-23) and the IL-23 specific p19 subunit, but not p35 subunit of IL-12. There is also evidence of increased expression of Th17 specific CC chemokine receptor, CCR6 and its ligand CCL20 in psoriatic skin lesions, and IL-17 can induce the secretion of CCL20 from keratinocytes. Recently, the observations from genome wide association study (GWAS) strengthens the contribution of Th17 pathway in psoriatic disease. It has been found that polymorphisms in gene encoding IL-12B (IL12B), IL-23A (IL23A), IL-23R (IL23R), ACT1 (TRAF3IP2). These studies confirm IL-17 as a crucial proinflammatory cytokine for psoriasis. The most convincing evidence regarding the role of Th17 in psoriasis comes from the success of preclinical and clinical studies targeting p40IL-12/IL-23 and IL-17/IL-17R system. We will discuss about this in our next section. In the pathogenesis of psoriasis, IL-17 regulates several crucial pathological events (Fig. 1): a) IL-17 contributes in recruiting neutrophils to the epidermis of psoriatic lesion by upregulating neutrophil specific chemokines; b) recruits more pathogenic Th17 cells by modulating CCL20 release from keratinocytes; c) induces expression...
Antigen presenting cells; CCL20, chemokine CC motif ligand 20; CXCL, Chemokine (C-X-C motif) ligand; MMP, matrix metalloproteinase.

β of relevant antimicrobial peptides of psoriasis such as β-defensin, S100A7, S100A8, S100A9, which in turn act as pro-inflammatory stimulus;\textsuperscript{104,120} contributes to disruption of skin barrier by downregulating expression of filaggrin and adhesion molecules in keratinocytes;\textsuperscript{121} d) IL-6 production in fibroblasts and dendritic cells are increased with IL-17, leading to more commitment of T cells to Th17 phenotype and perpetuates the inflammatory cascade; e) IL-17 induces TNFα release form dendritic cells and macrophages.\textsuperscript{104}

Psoriatic arthritis (PsA) is a common comorbidity of psoriasis. The etiopathogenesis of PsA is not known completely. Almost 30 % of psoriasis patients suffer from psoriatic arthritis.\textsuperscript{6} Psoriasis and PsA shares few immunological events in their pathogenesis. Skin and synovium in psoriasis and PsA respectively are characterized by the infiltration of immune cells including T cells, dendritic cells, neutrophils and macrophages.\textsuperscript{122-124} The success of anti-TNF therapy in PsA indicates that, rheumatoid arthritis and PsA shares some common pathway of joint damage,\textsuperscript{125-127} although these two are clearly different diseases, and can be distinguished according to their clinical, radiologic, and serologic features.\textsuperscript{128} CD4+ T cells predominate over CD8+ cells in the synovial membrane of PsA joints\textsuperscript{129} and the reverse is in the synovial fluid.\textsuperscript{130} In contrast to psoriasis, very few studies have shown the role of IL-17 and its receptor in psoriatic arthritis. In a study, Jandus C et al showed abundance of Th17 cells in the circulation of PsA patients.\textsuperscript{131} Our research group have shown the pathogenic role of IL-17 in psoriatic disease. We observed that skin, synovial tissue and synovial fluid of patients with psoriasis and PsA are enriched with Th17 cells. Further, we found that Th17 cells appears early in the developing psoriatic lesions, and were well maintained in the psoriasis xenograft on SCID mouse model. In PsA, we found significantly more IL-17 producing CD4+ T cells in the synovial fluid and synovial tissue of PsA patients. We also observed upregulation of IL-17R in synovial fibroblast of PsA patients compared to osteoarthritis and meniscal tear patients. This IL-17/IL-17R system is functionally active in PsA, and blocking of IL-17R with a monoclonal antibody abrogated the IL-17 induced release of pro-inflammatory cytokines (IL-6, IL-8) and MMP3.\textsuperscript{27} We can assume that similar to rheumatoid arthritis, IL-17 might play a role in bone erosion through inducing RANKL.\textsuperscript{132,133} Here also, the therapeutic success of anti-IL-17 therapy in PsA further proves the role Th17 in PsA.

Role of IL-17 in vascular remodelling

Several studies have shown increased risk of cardiovascular morbidity in patients with severe psoriasis, and this is partly attributed to accelerated atherosclerosis in these patients.\textsuperscript{134-138} Although there are some inconsistency in relating the cardiovascular morbidity in psoriatic disease,\textsuperscript{139,140} herein we are not discussing that issue. So far, the more common belief is that severe psoriasis is associated with increase rate of endothelial dysfunction, atherosclerosis and cardiovascular morbidity. The carotid intima media thickness (CIMT) and plaque frequency are commonly used as risk markers of subclinical atherosclerosis.\textsuperscript{141} Studies have shown that duration and severity of psoriasis is associated with subclinical atherosclerosis as determined by CIMT.\textsuperscript{142-144} The premature atherosclerosis and endothelial dysfunction is attributed to the effect of systemic inflammation on endothelial cell mediated functions. It has been show that use of TNF inhibitor reduced the risk of cardiovascular events and atherosclerosis in rheumatoid arthritis and psoriatic patients.\textsuperscript{145,146} In this context, recent studies have shown the role of IL-17 in endothelial dysfunction and subsequent atherosclerosis. Hot et al showed that IL-17 alone has procoagulant and prothrombotic effect, and these effects of IL-17 heightens in presence of TNFα.\textsuperscript{147} In another study with rheumatoid arthritis patients, Marder et al showed the introduction of IL-17 in endothelial dysfunction and cardiovascular risk.\textsuperscript{148} In unstable angina and acute myocardial infarction patients, serum IL-17 concentration was found to be elevated.\textsuperscript{149} IL-17 along with IFN-γ were more produced in disease coronary artery compared to non diseased vessels, and induces proinflammatory responses in
the vascular smooth muscle cells, by recruiting monocytes/macrophages. In human atherosclerotic plaque, existence of resident plaque cells expressing constitutively IL-17E, B cells and neutrophils expressing IL-17 suggesting the role of IL-17 in atherosclerosis. These observation were further confirmed in mice experiments. These in vitro and in vivo observations indicate the pathogenic role of IL-17 in atherosclerosis and cardiovascular morbidities, which are seen in psoriatic and other autoimmune diseases. Thus, inhibiting IL-17/IL-17R signalling system can decrease the incidence of subclinical atherosclerosis and cardiovascular comorbidities. Future studies in this direction will confirm this hypothesis.

**IL-17/IL-17R system, a potential therapeutic target in psoriatic disease**

As we have discussed previously that the most compelling evidence regarding the role of IL-17/IL-17R in psoriatic disease came from the therapeutic success of preclinical and clinical studies targeting this pathway. Biologics are becoming the most important therapeutic tool in treatment of autoimmune diseases including psoriasis. The journey of biologics started almost two decades ago with TNFα inhibitors, which changed immensely the prognosis of many autoimmune diseases including rheumatoid arthritis, psoriatic disease, ankylosing spondylitis. IL-17 and TNFα have few synergistic effects, and studies showed that nonresponders to anti-TNF therapy has upregulated genes associated with IL-17 pathway, suggesting anti-IL-17 therapy as an alternative in TNFα inhibitor non-responders.

In search for new biologics apart from TNFα, scientists decided to target the IL-23/Th17 pathway keeping in mind its crucial role in autoimmune diseases. IL-12/IL-23 p40 subunit was used as a therapeutic target for this pathway. Ustekinumab, a human monoclonal antibody targeting shared p40 subunit of IL-12 and IL-23, showed significant improvement in clinical trials, and got approval for use in moderate to severe plaque psoriasis. Briakinumab (ABT-874) is another IL-12/IL-23 targeted antibody, which showed much promise in phase II and III clinical trials in psoriasis, but was withdrawn by the manufacturer in 2011. The IL-12/IL-23 targeted therapy raised some safety concern due to more number of reported major adverse cardiovascular events (MACE: a combined end point of myocardial infarction, cerebrovascular accident or cardiovascular death) in the psoriasis patients received either ustekinumab or briakinumab compared to placebo or TNF inhibitor treated group. In a meta-analysis comprising of 22 randomized clinical trials, Ryan et al showed the increased number of MACE in ustekinumab or briakinumab treated patients. Briefly, in the placebo-controlled phases of clinical trials, 3,179 patients received either of these biologics and 10 of them (ustekinumab = 5 and briakinumab = 5) had MACE compared with zero events in the placebo group (1,474 patients). In contrast, in studies of anti-TNFα drugs, only 1 of the 3,858 patients had a MACE compared with the same number in the placebo group (1,812 patients). Considering all phases of clinical trials till date, total 53 MACEs have been reported; 26 MACEs in studies of ustekinumab and 27 MACES in studies of briakinumab. In this meta-analysis, compared to the placebo the authors did not find significant increase in MACEs in the anti-IL-12/23 treated group, but they stated that this study may have been underpowered to identify a significant difference. In another meta-analysis, Tzellos et al showed a likelihood of increase risk of MACEs in psoriasis patients treated with anti-IL-12/23 therapy compared to placebo. In contrast, Papp et al showed the 5 year safety profile of ustekinumab with no significant increase in MACEs. They have further reported that there was no dose related cumulative toxicity and the overall mortality and malignancies were comparable as seen in the general U.S. population. Apart from these two anti-IL-12/23 biologics, another agent (SCH-900222) targeting p19 subunit of IL-23 is in phase II clinical trial for moderate to severe plaque psoriasis.

Now, we will discuss in brief about the ongoing clinical trials with several compounds targeting the IL-17/IL-17R system in psoriasis (Fig. 2; Table 1). Two monoclonal
IL-17 and IL-17R: an auspicious therapeutic target for psoriatic disease

Table 1 List of IL-23 and IL-17 targeted biologics in clinical trial for psoriatic disease

<table>
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<th>New drugs</th>
<th>Therapeutic target</th>
<th>Manufacturer</th>
<th>Phase</th>
<th>Status</th>
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<td>Novartis Pharmaceuticals</td>
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<td>IL-17A</td>
<td>Eli Lilly and Company</td>
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<td>Ongoing</td>
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<td>NCT01540760</td>
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<td>SCH 900222/MK-3222</td>
<td>IL-23p19</td>
<td>Merck</td>
<td>III (psoriasis)</td>
<td>Ongoing</td>
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1. Secukinumab is a fully human IgG1κ IL-17A specific monoclonal antibody and has recently published the phase III results in psoriasis and is currently in phase III for psoriatic arthritis. In a recently published phase III study, the efficacy and safety of secukinumab was assessed in moderate to severe plaque psoriasis patients. A total of 2044 patients were studied in two phase III studies: ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis), which included 738 patients, and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis), which included 1306 patients. The patients were randomly assigned to subcutaneous secukinumab at a dose of 300 mg or 150 mg (administered once weekly for 5 weeks, then every 4 weeks), placebo, or (in the FIXTURE study only) etanercept at a dose of 50 mg (administered twice weekly for 12 weeks, then once weekly). The primary endpoint of this study was achievement of at least 75% improvement from baseline in the Psoriasis Area and Severity Index score (PASI 75), and the secondary end points were Investigator’s Global Assessment (coprimary endpoints). It was found that 75 mg and 150 mg of Secukinumab resulted in significant decrease in PASI 75 response rates (57% and 82% respectively) compared to placebo (9%). In the follow up period, higher PASI 75 response rates were maintained compared to placebo. At week 12, the 150 mg group showed significantly higher PASI 90 response rate compared to placebo (52% vs. 5%) and retained this effect during the follow-up period. Overall, secukinumab was well tolerated. The serious adverse event (SAE) was s more or less same between the treatment and placebo group. Among the other adverse events, headache, upper respiratory tract infections and back pain occurred more in the treatment group compared to placebo. In the highest dose arm, two patients experienced a transient decrease in neutrophil count at a single time point. The study concluded that subcutaneous secukinumab treatment (75 mg and 150 mg) significantly improves the plaque psoriasis in terms of PASI 75 with minimal toxicity. Similarly in a proof-of-concept phase II trial, secukinumab was given to 28 active psoriatic arthritis patients and the ACR20 response was evaluated at week 6. Although secukinumab could not reach statistically significant ACR20 response at week 6 compared to placebo, but the clinical response, ESR, CRP and quality of life showed more favourable effect in secukinumab group compared to placebo. Phase III studies with secukinumab in psoriatic arthritis is going on.

2. Ixekizumab (LY2439821) is a humanized IgG4 monoclonal antibody targeting IL-17A. This biologic is in phase III clinical trial for psoriasis and psoriatic arthritis. In a recently published phase II study, ixekizumab showed significant improvement in plaque psoriasis compared to placebo. Briefly, in this phase II study, 142 patients with moderate to severe plaque psoriasis were assigned randomly to receive subcutaneous injections of different doses of ixekizumab (10, 25, 75 or 150 mg) or placebo at 0, 2, 4, 8, 12 and 16 weeks. The primary endpoint was the percentage of patients achieving PASI 75 at 12 weeks. The secondary end points were PASI 90 and PASI 100 at 12 weeks. The study found that all doses of ixekizumab except 10 mg achieved > 75% PASI 75. The clinical improvement in the treatment arms occurred as early as at 1 week, and persisted through 20 weeks. The
adverse event rates were comparable in all the groups and no serious adverse events were reported.

3. Brodalumab is a human IgG2 anti-IL-17RA monoclonal antibody, binds IL-17RA with high affinity. In addition to IL-17A, IL-17RA subunit is required for signalling of IL-17F, and IL-17A/IL-17F heterodimer.80,81 Thus inhibition of IL-17RA leads to inhibition of IL-17A, IL-17F, IL-17A/F signalling pathway. Thus, this biologic has a broad spectrum inhibition on IL-17 mediated signalling pathway, compared to other IL-17A targeted therapy which focus only on IL-17, spares the IL-17F and IL-17A/IL-17F heterodimer. Brodalumab is in different phases of clinical trial for psoriasis and psoriatic arthritis.116,172 In a recently published phase II study, brodalumab showed significant improvement in psoriasis compared to placebo.116 Briefly, in this phase II clinical trial, 198 moderate to severe psoriatic patients were randomized to receive subcutaneous brodalumab (70 mg, 140 mg, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 or 280 mg monthly) or placebo. The primary endpoint was the percentage improvement in PASI from baseline at week 12. The secondary end points were percentage of patients achieving PASI 75 and PASI 90 at 12 weeks. An improvement of at least 75% and at least 90% in the PASI score at week 12 was seen in 77% and 72%, respectively, of the patients in the 140-mg brodalumab The commonly reported adverse events were upper respiratory tract infection, nasopharyngitis and injection site reaction.

Apart from developing new biologics targeting Th17 pathway, generous efforts have been put to target signalling pathway of Th17 differentiation using small molecules. A recent study showed that use of digoxin and its synthetic derivative can inhibit the Th17 differentiation by suppressing RORγt, suggesting a new Th17 pathway therapeutic target for autoimmune diseases.173 In another studies it has been shown that high affinity synthetic ligand of RORα and RORγt, SR1001 and ursolic acid effectively inhibited the differentiation of Th17 cells and thus dampen the mouse autoimmune diseases.174,175 Recent studies have shown that, PI3K/Akt/mTOR cascade contributes in Th17 differentiation, thus targeting specific isoform of PI3K will serve as a therapeutic candidate for Th17 pathway.176-178 In this context, our research group has shown that IL-17, IL-22 exerts their mitogenic effect on keratinocytes (key effector cells in psoriasis) and synovial fibroblasts (key effector cells in psoriatic arthritis) through PI3K/Akt/mTOR cascade, suggesting the therapeutic potential of key kinases of this cascade in psoriatic disease.90,179

Safety concern of IL-17 targeted therapy

In the preclinical and clinical studies, IL-17 targeted therapy did not show any major safety concern so far. But before finalizing our comment we wish to see the safety profile in more number of patients. IL-17 exerts its protective effect against extracellular gram positive and gram negative bacteria and fungi, it does not affect the intracellular pathogens such as Mycobacterium tuberculosis or Listeria monocytogenes.78,98,99,102 Thus, compared to TNFα, it is not expected to have higher rate of tuberculosis with IL-17 targeted therapy. As IL-17 has a crucial role in survival, expansion and migration of neutrophils, the increase susceptibility to infection with anti-IL-17 therapy can be attributed to the abnormal neutrophil response in absence of IL-17.96,97 Thus, the chance of bacterial and fungal infection is theoretically more with IL-17 targeted therapy. In animal experiments it has been demonstrated that defect in IL-17/IL-17R increases the incidence and severity of bacterial and fungal infections.96,100,101 At this stage of drug development, few incidences of neutropenia, upper respiratory tract infections, headache have been documented, but none of them were severe enough to withhold the drug development.116,117 Although, few cases of local candida infections have been reported, but the contribution of IL-17 inhibition still need to be clarified.115,181

Conclusion

Though IL-17 was known for last two decades, but its pathogenic role in human diseases became more prominent after the discovery of Th17 cells. In last one decade, several studies have strongly established the regulatory role of Th17 cells and its signature cytokine, IL-17 in mouse and human autoimmune diseases including rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease. The increased expression of IL-17 in the serum, lesional skin and synovial tissue of psoriasis and psoriatic arthritids patients respectively suggest the functional significance of this relatively new cytokine. Later on several in vitro and in vivo studies dissected out the regulatory role of IL-17 in the pathogenesis of different human autoimmune diseases. The most compelling evidence of the functional relevance of IL-17 in human autoimmune diseases arise from the observations made in preclinical and clinical trials with IL-17 targeted therapy. IL-17 and its receptor subunit, IL-17RA seems to be a potent therapeutic target in autoimmune diseases including rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis. At this stage of drug development, few clinical trials are going on with different monoclonal antibodies targeting either IL-17 or its receptor IL-17RA. Till date, data from this clinical trial showed promising results without much increase in infections/neoplasm. Future clinical trials of IL-17 targeted therapy with large number of patients will provide more insight about the safety profile of these new biologics.

Conflicts of interest

All the authors of this review article declare no competing interests.

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