

REVIEW ARTICLE

Iran J Allergy Asthma Immunol
June 2015; 14(3):246-254.

Th22 Cells Contribution in Immunopathogenesis of Rheumatic Diseases

Gholamreza Azizi¹, Anita Simhag², Nadia M.M.El Rouby³, and Abbas Mirshafiey⁴

¹ Imam Hassan Mojtaba Hospital, Alborz University of Medical Sciences, Karaj, Iran

² Karolinska Institutet Science Park AB, Huddinge, Sweden

³ Department of Histology, Dubai Medical College, Dubai, UAE

⁴ Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Received: 31 March 2014; Received in revised form: 13 June 2014; Accepted: 10 July 2014

ABSTRACT

Newly identified T helper cell 22 (Th22) is a subset of CD4⁺T cells with specific properties apart from other known CD4⁺ T cell subsets with distinguished gene expression and function. Th22 cells are characterized by production of a distinct profile of effector cytokines, including interleukin (IL)-22, IL-13, and tumor necrosis factor- α (TNF- α). The levels of Th22 and related cytokine IL-22 are increased in various autoimmune diseases and positively associated with some rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, behcet's disease, ankylosing spondylitis and psoriatic arthritis. In summary, IL-22 and Th22 cells play a significant and complicated role in inflammatory and autoimmune rheumatic diseases, therefore, targeting IL-22 or Th22 have unique and attractive advantages due to the fact that Th22 subset is recently identified and its associated research is extremely limited. This review discusses the role of Th22 and its cytokine IL-22 in the immunopathogenesis of rheumatic disease.

Keywords: IL-22; Rheumatic disease; Rheumatoid arthritis; Systemic lupus erythematosus; Th22

INTRODUCTION

Rheumatic disease (rheumatism) is a general term used to describe more than 100 items that affect the muscles, joints, connective tissues, soft tissues around the joints, and bones. These painful disorders are usually caused by inflammation, swelling, and pain in the joints or muscles. There is evidence that the classes and subclasses of cellular arms of immune system and

inflammation phenomenon are implicated in rheumatic diseases.¹

One of the main cells of immune system that is implicated in autoimmune diseases is CD4⁺ T helper (Th) cells. These cells can differentiate into one of several subclasses, including Th1, Th2, Th3, Th9, Th17, and Th22 which produce different cytokines and chemokines to promote a specific type of immune response.² In recent years, our knowledge of CD4⁺ T cell differentiation has significantly increased, and to date the new subsets continue to be recognized.³ It is suggested that the differentiation of naive CD4⁺ T cells into lineages with distinct effector functions is an

Corresponding Author: Abbas Mirshafiey, PhD;
Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran-14155, Box: 6446, Iran.
Tel: (+98 21) 8895 4913, E-mail: mirshafiey@tums.ac.ir

irreversible event. However, following the recognition of new subsets, there is an expanded recognition of plasticity.^{4,5} Larsen et al. reported that despite the pronounced functional differences, there is extensive T-cell receptor (TCR) $\alpha\beta$ sharing in all the effector and regulatory subsets defined. They also revealed that a naive precursor T cell is able to adopt multiple Th-subset profiles irrespective of antigen specificity.⁶ Other studies show that mouse Th17 cells are not a stable T-cell subset, and can transform into Th1 and Th17 cell subsets *in vitro* and *in vivo*.⁷⁻⁹ Lexberg et al. in 2010 revealed that *ex vivo* isolated Th17 cells can be converted into Th1/Th17 cells by combined interleukin (IL)-12 and interferon (IFN)- γ signaling. Additionally, Th1/Th17 cells, stably co-express transcriptional factors ROR γ t and T-bet at the single-cell level.⁷ Similarly, Kurschuset al. in another study showed that Th1 cells could be converted *in vivo* to IL-17A/IFN- γ co-expressing cells in the mouse mesenteric lymph nodes.⁸ Although T cell plasticity is now an accepted component of the specific immune system, the stability of a T cell phenotype over numerous cell divisions remains a hallmark of CD⁺Th cell subsets, conferring immunologic memory, as Eyerich et al. have demonstrated for Th22 cell clone. They proposed that Th22 cells indicate a stable T cell lineage, and memory Th22 cells do not transform into another subset.¹⁰ *In vitro*, skin-derived memory Th22 clones did not lose the capacity to produce IL-22 under Th1, Th2, Th17, and regulatory T (Treg) conditions, however, IFN- γ was slightly produced under different conditions.¹⁰ Shen et al. found that unlike memory Th22 clones, Th22 cells in the early stage of development maintained their differentiation program *in vitro* and could be reprogrammed into Th1 and Th17 cell subsets, but not Th2 cells. They showed that Th22 cells slowly lost their IL-22 expression and transformed into Th17 cells in a transforming growth factor (TGF)- β dependent manner. These findings, although suggesting the flexibility of Th22 cells, but also indicate active maintenance of their program *in vivo*.¹¹

Th22 Cells

The newly identified CD4⁺ T cell subtype, Th22 cells, are characterized by production of a distinct profile of effector cytokines, including IL-22, IL-13, and tumor necrosis factor (TNF)- α . Similar to Th17 cells, Th22 cells express IL-22, CCR4, and CCR6; they also express other factors including fibroblast growth

factor isoforms involved in tissue remodeling and chemokine receptor CCR10. CCR4 and CCR10 expression drives Th22 cells to migrate to the skin.¹² On the other hand, Th22 cells do not express IL-17, IL-23 R, CCL20, CD161 (Th17 markers), IFN- γ (Th1 marker) and IL-4 (Th2 marker). In addition, Th22 cell subset is distinguishable from Th17 cells by low CD161 expression and a high degree of polyfunctionality.⁶ Collectively, these characteristics distinguish Th22 cells as a novel T helper cell lineage from the Th17, Th1 and Th2 subtypes.^{10,13} Activated naive CD4⁺ T cells can differentiate to Th22 cells in the presence of IL-6 and TNF- α . However, this differentiation could be prevented by the addition of increasing concentrations of TGF- β .¹⁴ Also Th22 cells do not express the Th1-, Th2- and Th17-associated transcription factors T-bet, GATA-3 and ROR γ t, respectively.¹⁵ However, Duhon et al. reported that Th22 had low or undetectable expression of these transcription factors.¹⁵ The Th22 expansion appears to be regulated by discrete transcription factor named the aryl hydrocarbon receptor (AHR), due to the fact that intracellular molecular mechanism involved in Th22 differentiation aren't fully characterized and additional intracellular molecules still being investigated.¹⁶ Alamet al. demonstrated that Notch signaling drives IL-22 secretion in CD4⁺ T cells by stimulating the AHR. Moreover, Notch-mediated stimulation of CD4⁺ T cells increased the production of IL-22 even in the absence of STAT3.¹⁷ Baba et al. showed that the AhR ligand VAF347 selectively acts on monocytes and naive CD4⁺Th cells to promote the development of Th22 cells and it suppressed the generation of the either Th1 or Th17 cells.¹⁶ In a similar study, it was found that dioxin, as a high affinity and stable AHR-ligand, as well as the natural AHR-ligand 6-formylindolo(3,2-b)carbazole induced the down-stream AHR-target cytochrome, and without affecting IFN- γ , they enhanced IL-22 production while simultaneously decreased IL-17A production by CD4⁺ T cells. Furthermore, the specific AHR-inhibitor CH-223191 abrogated these effects. Importantly, AHR-ligation not only decreased the Th17 cells number but also primed naive CD4⁺ T cells to generate IL-22 without IL-17 and IFN- γ .¹⁸ This confirms previous findings by Trifari et al. that demonstrated down-regulation of either transcription factors, AHR or the RORC by RNA-mediated interference which affected IL-22 production, while IL-17 production was affected just by down-

regulation of RORC by RNA-mediated interference. Further, AHR agonists substantially changed the balance of IL-22- versus IL-17-producing Th cells.¹²

Th22 cells could be differentiated by stimulation of naive CD4⁺ T cells in the presence of conventional dendritic cells (DCs) and/or plasmacytoid DCs. By using activated conventional DCs and plasmacytoid DCs, Trifari et al. have revealed that human DCs actually induce the development of Th22 cells from naive CD4⁺T cells. Accordingly, plasmacytoid DCs were more powerful than conventional DCs in the expansion of Th22 cells. However, it was unknown whether tissue DCs, were really capable to induce unique Th22 population.¹² It was revealed that Th22 cells could be differentiated by plasmacytoid DCs in the presence of TNF- α and IL-6, both of which are commonly produced by DCs during their maturation. In addition, Langerhans cells as specialized professional antigen-presenting cells (APCs) found in the epidermis, are qualified to induce Th22 cells.^{12,15,19} Accordingly, in a recent study, Duluc et al. demonstrated that both Langerhans cells and CD14⁺ lamina propria-DCs are potent inducers of Th22 in the human vaginal mucosa.²⁰ In vitro, when Th22 cell clones were cultured in Th1-, Th2-, Th17- or Treg-polarizing conditions, appeared to be fully stable and continued to express IL-22 and no other cytokines associated with other T CD4⁺ subsets.¹⁰

IL-22, also known as IL-10-related T cell-derived inducible factor (IL-TIF) is a member of a group of cytokines called the IL-10 family or IL-10 superfamily (including IL-19, IL-20, IL-24, and IL-26). IL-22 was initially identified as a gene induced by IL-9 in mouse T cells and mast cells. The IL-22 mature protein shares approximately 79% and 22% amino acid sequence identity with mouse IL-22 and human IL-10, respectively.²¹ IL-22 was originally explained as a Th1-associated cytokine, IL-22 has since been shown to be produced basically by Th17 and Th22 cells.^{12,22} In fact, newest data have shown that IL-22 production among CD4⁺ T cells is more closely related to IFN- γ than IL-17, indicating that IL-17 and IL-22 are differentially regulated during CD4⁺ T cell differentiation.²³

IL-22 is also expressed by CD8⁺ T cells and IL-22⁺CD8⁺ T-cell frequency correlated with atopic dermatitis disease severity.²⁴ Furthermore, other innate immune cells such as mast cells, CD11c⁺DCs, $\gamma\delta$ T cells, NKT cells and natural killer 22 (NK22) cells are able to produce IL-22. NK22 is a human NK cell subset

located in mucosa-associated lymphoid tissues, such as tonsils and Peyer's patches, which is hard-wired to secrete IL-22, IL-26 and LIF (leukaemia inhibitory factor). The NK22 cells are triggered by acute exposure to IL-23. In vitro, NK22-secreted cytokines stimulate epithelial cells to produce IL-10, proliferate and express a variety of mitogenic and anti-apoptotic mediators. NK22 cells are also found in mouse mucosa-associated lymphoid tissues and are seen in the lamina propria during bacterial infection, suggesting that NK22 cells are an innate source of IL-22 that may constrain inflammation and protect mucosal sites.²⁵

Th22 cells produce IL-22 in response to TNF- α and IL-6, especially in the skin, whereas innate lymphoid $\gamma\delta$ T cells produce IL-22 in response to IL-23, particularly in the lung. NK cells produce IL-22 in response to IL-12 and IL-18 or IL-23. ROR γ t-positive innate lymphoid cells, including lymphoid tissue inducer (LTi) and LTi-like cells express IL-22 with IL-23 again enhancing expression.²⁶

IL-22 affect on target cells through a class II cytokine receptor composed of an IL-22-binding chain, IL-22RA1 (also called ZcytoR11/CRF2-9) and the IL-10RB (CRF2-4) subunit, which is shared with the IL-10R.^{27,28} IL-22, although is produced by immune cells, it is known that neither resting nor activated immune cells express IL-22 receptor, moreover IL-22 has no effect on these cells in vivo and in vitro. In contrast, IL-22 regulates the function of certain tissue cells, including cells of the skin, kidney, and the digestive (pancreas, small intestine, liver, and colon), and respiratory (lung and trachea) systems representing putative targets for this cytokine.²⁹

Several cell types, in particular epithelial cells, express receptor for the cytokine IL-22 and upon its recognition produce molecules that are active both locally and systemically.³⁰ Lejeune et al. analyzed the signal transduction pathways activated in response to IL-22 and found that IL-22 induced activation of Tyk2 and JAK1 but not JAK2, as well as phosphorylation of STAT1, STAT3, and STAT5. Using antibodies specific for the phosphorylated form of MEK1/2, ERK1/2, p90RSK, JNK, and p38 kinase, they showed that IL-22 activates the three major MAPK pathways.³¹ While common factors such as STAT3 and ROR γ t drive the expression of both IL-22 and IL-17 cytokines whereas other factors, such as c-Maf act specifically on IL-22.³²

The IL-22 expression allows Th22 cells to primarily affect on epithelial and stromal cells including skin

keratinocytes, intestinal and respiratory epithelial cells, hepatocytes, pancreatic acinar cells, colonic sub epithelial myofibroblasts and synovial fibroblasts derived from patients with RA, where the Th22 cells appear to provide a protective role in regulating wound repair and healing in the skin, lung and gut.¹⁵ Overall, IL-22 does not serve the communication between immune cells but it is a T cell mediator that directly improves the innate nonspecific immunity of the above mentioned tissues.²⁹ Although IL-22 is beneficial to the host in many infections and inflammatory disorders, depending on the target tissue it could be pathogenic due to its inherent pro-inflammatory properties, which are further enhanced when IL-22 is secreted together with other pro-inflammatory cytokines, in particular IL-17.³² In addition, IL-22 is known to be expressed by Th22 in several inflammatory rheumatic diseases, including, rheumatoid arthritis (RA),³³ systemic lupus erythematosus (SLE),³⁴ systemic sclerosis,¹³ Behcet's disease,³⁵ ankylosing spondylitis (AS),³³ and psoriatic arthritis.³⁶

RA

RA is a chronic inflammatory disease characterized by the sequestration of various leukocyte subpopulations within both the developing pannus and synovial space. This inflammatory disease targets first the synovium, or lining of the joint, resulting in pain, stiffness, swelling, damage, and loss of function of the joints. The chronic nature of this disease results in inflammation of multiple joints, with subsequent destruction of the joint cartilage and erosion of bone.³⁷ The immunological mechanisms in RA consist of dysfunctional cellular and humoral immunity, enhanced migration and attachment of peripheral macrophages and inflammatory leukocytes to the synovium. In RA, synovium consists greatly of macrophages (30-40%), T cells (30%) and synovial fibroblasts as well as other immune cells.³⁸ CD4⁺ T helper cells play critical roles in the development and progression of RA. Identification of Th17 cells led to breaking the dichotomy of the Th1/Th2 axis in immunopathogenesis of RA.³⁷

Recently, Th22 cell as a new subset of CD⁺4 T cells have been implicated in the pathogenesis of RA. However, the roles of this subset in the pathophysiology of RA are still being investigated. For the first time, in 2011 Zhang et al. reported that the elevated Th22 cells was correlated with Th17 cells in

patients with RA. In this experiment, Th22 cells, pure Th17 cells (CD4⁺IFN- γ IL-22⁻IL-17⁺ T cells), Th17 cells (CD4⁺IL-17⁺T cells), and IL-22 were significantly raised in RA patients compared with osteoarthritis and healthy controls, but there were no significant differences regarding Th1 cells and IL-17. In addition, Th22 cells showed a positive correlation with IL-22 and pure Th17 cells or Th17 cells in RA patients.³⁹ one year later in another study, Zhang et al. examined the frequencies of Th22 cells, Th17 cells and Th1 cells in peripheral blood from patients with AS and patients with RA compared with both patients with osteoarthritis as well as healthy controls. They confirmed their previous finding and reported that Th22 cells, Th17 cells and IL-22 were significantly elevated in AS and RA patients compared with osteoarthritis patients and healthy controls. In addition, Th22 cells showed positive correlation with Th17 cells and IL-22 in AS and RA patients, however, the percentages of both Th22 cells and Th17 cells in peripheral blood were correlated positively with disease activity only in RA patients not in AS patients.³³ Van et al. confirmed above findings, and showed that peripheral Th17 and Th22 cell populations were increased in RA patients and present in RA synovial fluid. However, they displayed that primary peripheral blood and synovial Th17 cells were more potent in the stimulation of inflammatory IL-6, IL-8, MMP-1 and MMP-3 production by RA synovial fibroblasts (RASf) compared with Th22 cells. These findings display that IL-17A/Th17 cell-mediated synovial inflammation is independent of Th22 cells and its cytokine IL-22.⁴⁰ Conversely, Zhao et al. demonstrated that in the RA patients the percentages of Th22 cells are correlated positively with the levels of plasma IL-22⁴¹ and, a positive correlation between plasma IL-22 and Th17 cells was only found in AS patients not in RA patients.³³ In RA patients, apart from activated IL-22⁺ CD4⁺ T-cells, the IL-22 is mainly produced by mast cells, macrophages and synovial fibroblasts, and promotes inflammatory responses in synovial tissues by inducing the proliferation and chemokine production of synovial fibroblasts. Fibroblast-like synoviocytes (FLSs) are main players in the pathogenesis of synovitis in rheumatic diseases. IL-22 and IL-22R1 are expressed constitutively in FLSs.⁴² Finally, IL-22 is elevated in patients' sera with established RA, and the presence of bone erosions is associated with high IL-22 levels. Likewise, the elevation in serum level of IL-22

allows discrimination between patients with different clinical and laboratory determinants as well as shows the potential of IL-22 as a supplementary tool for increasing RA activity, especially in patients with rheumatoid factor (RF) antibodies (RF positivity was correlated with higher levels of IL-22 in patients with RA) and long-term disease.⁴³

SLE

Another rheumatic disease is SLE, an autoimmune disorder in which the immune system erroneously assaults healthy tissue throughout the body including skin, kidneys, joints, brain, and other organs. Immune system activation in SLE is characterized by a multitude of autoantibody production, complement activation, and immune-complex deposition, which cause tissue and organ damage. Therefore, lack of immune tolerance against self-antigens and extensive B-cell and T-cell responses are implicated in SLE pathogenesis.⁴⁴ With this introduction, a key feature of SLE is T cell dysfunction characterized by hyperresponsive antigen receptor signaling. Th cell abnormalities and cytokines produced by them are considered to be associated with the pathogenesis of SLE. Indeed, autoimmunity by Th cells could not be explained by Th1/Th2 cell paradigm. Th17 and Th22 cells producing the cytokines IL-17 and IL-22 may explain the progress and promotion of autoimmune phenomena.^{45,46} In a study, Zhao et al. in 2013 showed that the percentages of Th1, Th17 and Th22 CD4⁺ T-cells and the levels of plasma IL-22 and IL-17A in the SLE patients were significantly higher than that in the healthy subjects. In this investigation, the frequency of Th22 cells was correlated positively with that of Th17, but not with the other inflammatory values such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and C3 in SLE patients. These findings suggest that both Th17 and Th22 cells may participate in the SLE pathogenesis.⁴⁶ Recently, The Th22 cells and IL-22 have been more implicated in the pathogenesis of SLE. Cheng et al. suggested that the decreased plasma IL-22 levels, but not increased IL-17 and IL-23 levels, were correlated with disease activity in patients with SLE.⁴⁷ Subsequently Yang et al. suggested that Th22, but not Th17 might be a good index to predict the tissue involvement of SLE, although Th17 may play a role in the activity of SLE. The main findings focused on augmented Th22 cells and serum IL-22 levels in patients with sole lupus skin disease and reduced Th22

cells and serum IL-22 levels in patients with sole lupus nephritis. Additionally, the percentage of Th22 but not Th1 and Th17 cells has shown a positive correlation with IL-22 production and plasma IL-22 levels.^{34,48} In a study in 2014, Lin et al. revealed that the plasma IL-22 levels and its correlation with Th22 cells may be distinct features in new-onset of SLE compared to relapsing SLE patients. In new-onset SLE patients, IL-22 levels were significantly decreased compared to relapsing SLE patients and healthy subjects. After prednisone and hydroxychloroquine therapy, the level of plasma IL-22 in new-onset SLE patients was clearly augmented, however, it was still lower than healthy subjects. Moreover, in new-onset SLE patients high frequencies of plasma IL-22 autoantibodies were detected although, IL-22 levels had no correlation with IL-22 autoantibodies.⁴⁸

Spondyloarthritis

Spondyloarthritis or spondyloarthropathy is the name for a family of chronic immune-mediated inflammatory rheumatic diseases includes AS, psoriatic arthritis, reactive arthritis, undifferentiated arthritis and enteropathic arthritis.⁴⁹ T cells have been considered as pivotal items in triggering the disease and maintaining the immunopathogenesis process in the chronic phase. Like RA, the increased Th22 and Th17 cells either in blood, synovial fluid, or synovial tissues were also demonstrated in spondyloarthritis.⁵⁰ Romero-Sanchez et al. showed that IL-17, IL-23, IL-1, IL-6, and TNF- α levels were significantly higher in the serum of spondyloarthritis patients than healthy subjects, and there were no differences among spondyloarthritis subtypes. In synovial fluid, they found higher concentrations of cytokines, but only IL-23 showed significant differences. Therefore, higher levels of IL-23 in synovial fluid could propose local amplification of the Th17 cytokine profile.⁵¹

Other data explained that the frequency of Th17 as an IL-17 and IL-22 producing cells were increased in peripheral blood mononuclear cells (PBMCs) from patients with AS, resulting in secretion of higher quantities of IL-17 and IL-22 by PBMCs following stimulation.⁵² In addition, it was shown that among CD4⁺ lymphocytes and NKp44⁺ NK cell subsets, the latter were the major source of IL-22 on lamina propria mononuclear cells from AS patients, where it appears to play a tissue-protective role.⁵³

Psoriatic arthritis, is a type of arthritic inflammation

Th22 Cells in Rheumatic Diseases

characterized by a form of inflammation of the skin (psoriasis) and joints (inflammatory arthritis).⁵⁴ Increased frequencies of Th17 and Th22 cells are the feature of both psoriasis and psoriatic arthritis. However, their different distribution at disease tissues, including lower frequencies of IL-22⁺ CD4⁺ T cells in synovial fluid compared to skin and peripheral blood, and lack of IL-22 expression in synovial tissue indicate that Th17 and Th22 cells have a common role as well as divergent roles in the pathogenesis of psoriasis and psoriatic arthritis. Benham et al. demonstrated increased frequencies of Th17 cells in peripheral blood of patients with psoriasis and psoriatic arthritis. Their findings showed that IL-17 secretion was remarkably elevated in both psoriasis and psoriatic arthritis, whilst IL-22 secretion was higher in psoriatic arthritis compared to psoriasis and healthy controls.^{36,55} In patients with psoriatic arthritis, Th17 cell numbers were elevated in synovial fluid compared to peripheral blood. Moreover, increased frequencies of IL-17⁺ and IL-22⁺ CD4⁺ T cells were demonstrated in psoriasis skin lesions. In contrast, the increased frequency of Th17 cells was seen in psoriatic arthritis synovial fluid compared to peripheral blood whereas frequency of Th22 cells was lower. In conclusion, when IL-17 expression is equal in psoriatic arthritis, osteoarthritis and RA synovial tissue, IL-22 expression was higher in RA than either osteoarthritis or psoriatic arthritis synovial tissue, in which IL-22 was remarkably absent.³⁶

Behcet's Disease

Behcet's disease is a systemic inflammatory disorder characterized by recurrent episodes of oral ulceration, skin lesions, genital ulceration, and intraocular inflammation (uveitis).⁵⁶ Studies have shown that reduced levels of Tregs and augmented levels of Th1 and Th22 cells as well as Th17/Th1 cells might be associated with the immunopathogenesis of Behcet's disease.⁵⁷ In a study, Aktas et al. demonstrated that Th1, Th22 and IL-17A⁺IFN- γ ⁺-producing cells were significantly increased, and the percentage of Treg cells were dramatically reduced in Behcet's disease patients compared with healthy subjects. Additionally, the frequency of recurrent oral ulcers in Behcet's disease patients was correlated with increased Th22 cells.⁵⁷ IL-22 as principal cytokine of Th22 is associated with disease activity in Behcet's disease and associated with the presence of small vessel

inflammation, suggesting that IL-22 might be involved in its pathogenesis.⁵⁸ However, Na et al. suggest that in Behcet's disease patients, up-regulated IL-17 expression may also be associated with clinical activity of disease. Furthermore, in their study higher frequencies of IL-17 and IFN- γ expressing CD4⁺T cells were shown in patients with active Behcet's disease compared with healthy patients. Similarly, the levels of IL-17, IL-23, and IFN- γ in serum and culture supernatants were significantly elevated in these patients.⁵⁹

Uveitis in Behcet's disease is a major cause of vision loss through recurrent ocular inflammatory attacks.⁶⁰ It is revealed that IL-22 producing CD4⁺ T cells that react to self-antigens play a pivotal role in the immunopathogenesis of uveitis.³⁵ In a study by Cai et al. Behcet's disease with active uveitis displayed a significant higher expression of IL-22 in the culture supernatants of stimulated PBMCs and CD4⁺T cells in Behcet's disease within active uveitis compared with normal patients. Moreover, an increased frequency of IL-22-producing CD4⁺T cells was found in Behcet's disease patients with active uveitis.⁵⁸ It was confirmed by Sugita et al. in 2013, that Th22 clones from ocular samples taken from Behcet's disease patients produced large amounts of IL-22 and TNF- α , but not IFN- γ and IL-17. In addition, CD4⁺ T cells from the peripheral blood of Behcet's disease patients differentiated into Th22 cells in the presence of IL-6 and TNF- α in vitro. It was revealed that this polarized Th22 cell lines are able to produce a large amount of IL-22, and the polarized Th17 and Th1 cells can also produce IL-22. Furthermore, in mice with experimental autoimmune uveitis, IL-22-producing T cells secreted large amounts of IL-22 in the presence of retinal Antigen. These data suggest that IL-22 and TNF- α producing Th22 cells may play an important role in the ocular immune response in Behcet's disease.³⁵

CONCLUSION

Newly, Th22 cells were identified as a Th cell subset that produce IL-22 and TNF- α and are distinct from Th1, Th2, and Th17 cells. Th22 and its cytokine IL-22 are implicated in pathogenesis of rheumatic diseases, therefore, therapies based on the pharmacological signaling disruption of IL-22 could be useful for the treatment of rheumatic diseases.⁶¹ Treatment with recombinant cytokine or gene therapy

for of IL-22 may alleviate tissue destruction during inflammatory responses. It was demonstrated that in the presence of anti-TNF- α - and anti-IL-6-blocking antibody, Th22 cells failed to produce IL-22. Moreover, pretreatment with Th22 cells along with infliximab (a chimeric monoclonal antibody against TNF- α) produced less IL-22 and TNF- α .⁵⁵ Mitra et al. demonstrated successful inhibition of IL-22 induced fibroblast like synovocyte proliferation by anti-IL-22R antibody with blocking of IL-22/IL-22R interaction, which may be considered as a novel therapeutic target for psoriatic arthritis.⁵⁵ However, others believe that targeting IL-22 or Th22 might provide pathogenic treatment because, in one side it is difficult to generalize whether Th22 cell is protective versus pathogenic. On the other side, IL-22 function could not completely reflect Th22 function, since IL-22 apart from Th22 cells is also expressed by other cells. Accordingly, targeting Th22 or IL-22 is nonselective and may affect all of the Th22 and IL-22 in the whole body, leading unexpected side effects. However, it is suggested that the restricted expression of IL-22R1 in non-lymphoid cells could lead to a decrease of side effects mediated by immune responses.⁶¹ Therefore, further studies are required for clarifying the accurate role of Th22 and IL-22 in rheumatic diseases.

REFERENCES

1. Radenska-Lopovok SG. [Cell and cytokine markers in the synovial membrane in rheumatoid arthritis]. *Arkh Patol* 2013; 75(5):58-62.
2. Gutcher I, Becher B. APC-derived cytokines and T cell polarization in autoimmune inflammation. *J Clin Invest* 2007; 117(5):1119-27.
3. Li H, Rostami A. IL-9: basic biology, signaling pathways in CD4+ T cells and implications for autoimmunity. *J Neuroimmune Pharmacol* 2010; 5(2):198-209.
4. Zhou L, Chong MM, Littman DR. Plasticity of CD4+ T cell lineage differentiation. *Immunity* 2009; 30(5):646-55.
5. Nakayamada S, Takahashi H, Kanno Y, O'Shea JJ. Helper T cell diversity and plasticity. *Curr Opin Immunol* 2012; 24(3):297-302.
6. Larsen M, Arnaud L, Hie M, Parizot C, Dorgham K, Shoukry M, et al. Multiparameter grouping delineates heterogeneous populations of human IL-17 and/or IL-22 T-cell producers that share antigen specificities with other T-cell subsets. *Eur J Immunol* 2011; 41(9):2596-605.
7. Lexberg MH, Taubner A, Albrecht I, Lepenies I, Richter A, Kamradt T, et al. IFN-gamma and IL-12 synergize to convert in vivo generated Th17 into Th1/Th17 cells. *Eur J Immunol* 2010; 40(11):3017-27.
8. Kurschus FC, Croxford AL, Heinen AP, Wortge S, Ielo D, Waisman A. Genetic proof for the transient nature of the Th17 phenotype. *Eur J Immunol* 2010; 40(12):3336-46.
9. Lee YK, Turner H, Maynard CL, Oliver JR, Chen D, Elson CO, et al. Late developmental plasticity in the T helper 17 lineage. *Immunity* 2009; 30(1):92-107.
10. Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, Pallotta S, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. *J Clin Invest* 2009; 119(12):3573-85.
11. Shen W, Li W, Feigenbaum L, Hixon J, Durum S. Plasticity in the differentiation of IL-22 producing cells. *The Journal of Immunology*. 2013;190, (Meeting Abstract Supplement) 193.2.
12. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. *Nat Immunol* 2009; 10(8):864-71.
13. Truchetet ME, Brembilla NC, Montanari E, Allanore Y, Chizzolini C. Increased frequency of circulating Th22 in addition to Th17 and Th2 lymphocytes in systemic sclerosis: association with interstitial lung disease. *Arthritis Res Ther* 2011; 13(5):R166.
14. Cheng RH. [Expression level of Th22 cells and its cytokines in patients with acute lymphoblastic leukemia and its significance]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2013; 21(4):857-60.
15. Duhon T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. *Nat Immunol* 2009; 10(8):857-63.
16. Baba N, Rubio M, Kenins L, Regairaz C, Woisetschlager M, Carballido JM, et al. The aryl hydrocarbon receptor (AhR) ligand VAF347 selectively acts on monocytes and naive CD4(+) Th cells to promote the development of IL-22-secreting Th cells. *Hum Immunol* 2012 Aug;73(8):795-800.
17. Alam MS, Maekawa Y, Kitamura A, Tanigaki K, Yoshimoto T, Kishihara K, et al. Notch signaling drives IL-22 secretion in CD4+ T cells by stimulating the aryl hydrocarbon receptor. *Proc Natl Acad Sci U S A* 2010; 107(13):5943-8.

Th22 Cells in Rheumatic Diseases

18. Ramirez JM, Brembilla NC, Sorg O, Chicheportiche R, Matthes T, Dayer JM, et al. Activation of the aryl hydrocarbon receptor reveals distinct requirements for IL-22 and IL-17 production by human T helper cells. *Eur J Immunol* 2010; 40(9):2450-9.
19. Fujita H, Nograles KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG. Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proc Natl Acad Sci U S A* 2009; 106(51):21795-800.
20. Duluc D, Gannevat J, Anguiano E, Zurawski S, Carley M, Boreham M, et al. Functional diversity of human vaginal APC subsets in directing T-cell responses. *Mucosal Immunol* 2013; 6(3):626-38.
21. Dumoutier L, Van Roost E, Ameye G, Michaux L, Renauld JC. IL-TIF/IL-22: genomic organization and mapping of the human and mouse genes. *Genes Immun* 2000; 1(8):488-94.
22. Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol* 2007; 8(6):639-46.
23. Volpe E, Touzot M, Servant N, Marloie-Provost MA, Hupe P, Barillot E, et al. Multiparametric analysis of cytokine-driven human Th17 differentiation reveals a differential regulation of IL-17 and IL-22 production. *Blood* 2009; 114(17):3610-4.
24. Nograles KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol* 2009; 123(6):1244-52.
25. Cella M, Fuchs A, Vermi W, Facchetti F, Otero K, Lennerz JK, et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* 2009; 457(7230):722-5.
26. Takatori H, Kanno Y, Watford WT, Tato CM, Weiss G, Ivanov, II, et al. Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22. *J Exp Med* 2009; 206(1):35-41.
27. Boniface K, Bernard FX, Garcia M, Gurney AL, Lecron JC, Morel F. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. *J Immunol* 2005; 174(6):3695-702.
28. Xie MH, Aggarwal S, Ho WH, Foster J, Zhang Z, Stinson J, et al. Interleukin (IL)-22, a novel human cytokine that signals through the interferon receptor-related proteins CRF2-4 and IL-22R. *J Biol Chem* 2000; 275(40):31335-9.
29. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. *Immunity* 2004; 21(2):241-54.
30. Zenewicz LA, Flavell RA. Recent advances in IL-22 biology. *Int Immunol* 2011; 23(3):159-63.
31. Lejeune D, Dumoutier L, Constantinescu S, Kruijer W, Schuringa JJ, Renauld JC. Interleukin-22 (IL-22) activates the JAK/STAT, ERK, JNK, and p38 MAP kinase pathways in a rat hepatoma cell line. Pathways that are shared with and distinct from IL-10. *J Biol Chem* 2002; 277(37):33676-82.
32. Rutz S, Eidenschenk C, Ouyang W. IL-22, not simply a Th17 cytokine. *Immunol Rev* 2013; 252(1):116-32.
33. Zhang L, Li YG, Li YH, Qi L, Liu XG, Yuan CZ, et al. Increased frequencies of Th22 cells as well as Th17 cells in the peripheral blood of patients with ankylosing spondylitis and rheumatoid arthritis. *PloS one* 2012; 7(4):e31000.
34. Yang XY, Wang HY, Zhao XY, Wang LJ, Lv QH, Wang QQ. Th22, but not Th17 might be a good index to predict the tissue involvement of systemic lupus erythematosus. *J Clin Immunol* 2013; 33(4):767-74.
35. Sugita S, Kawazoe Y, Imai A, Kawaguchi T, Horie S, Keino H, et al. Role of IL-22- and TNF-alpha-producing Th22 cells in uveitis patients with Behcet's disease. *J Immunol* 2013; 190(11):5799-808.
36. Benham H, Norris P, Goodall J, Wechalekar MD, FitzGerald O, Szentpetery A, et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. *Arthritis Res Ther* 2013; 15(5):R136.
37. Azizi G, Jadidi-Niaragh F, Mirshafiey A. Th17 Cells in Immunopathogenesis and treatment of rheumatoid arthritis. *Int J Rheum Dis* 2013; 16(3):243-53.
38. Muller-Ladner U, Pap T, Gay RE, Neidhart M, Gay S. Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. *Nat Clin Pract Rheumatol* 2005; 1(2):102-10.
39. Zhang L, Li JM, Liu XG, Ma DX, Hu NW, Li YG, et al. Elevated Th22 cells correlated with Th17 cells in patients with rheumatoid arthritis. *J Clin Immunol* 2011; 31(4):606-14.
40. van Hamburg JP, Corneth OB, Paulissen SM, Davelaar N, Asmawidjaja PS, Mus AM, et al. IL-17/Th17 mediated synovial inflammation is IL-22 independent. *Ann Rheum Dis* 2013; 72(10):1700-7.
41. Zhao L, Jiang Z, Jiang Y, Ma N, Zhang Y, Feng L, et al. IL-22+ CD4+ T cells in patients with rheumatoid arthritis. *Int J Rheum Dis* 2013; 16(5):518-26.

42. Ikeuchi H, Kuroiwa T, Hiramatsu N, Kaneko Y, Hiromura K, Ueki K, et al. Expression of interleukin-22 in rheumatoid arthritis: potential role as a proinflammatory cytokine. *Arthritis Rheum* 2005; 52(4):1037-46.
43. da Rocha LF, Jr., Duarte AL, Dantas AT, Mariz HA, Pitta Ida R, Galdino SL, et al. Increased serum interleukin 22 in patients with rheumatoid arthritis and correlation with disease activity. *J Rheumatol* 2012; 39(7):1320-5.
44. Kiriakidou M, Cotton D, Taichman D, Williams S. Systemic lupus erythematosus. *Ann Intern Med* 2013; 159(7):ITC4-1.
45. Abou Ghanima AT, Elolemy GG, Ganeb SS, Abo Elazem AA, Abdelgawad ER. Role of T helper 17 cells in the pathogenesis of systemic lupus erythematosus. *Egypt J Immunol* 2012; 19(2):25-33. PubMed PMID: 23885404.
46. Zhao L, Jiang Z, Jiang Y, Ma N, Wang K, Zhang Y, et al. IL-22+CD4+ T-cells in patients with active systemic lupus erythematosus. *Exp Biol Med (Maywood)* 2013; 238(2):193-9.
47. Cheng F, Guo Z, Xu H, Yan D, Li Q. Decreased plasma IL22 levels, but not increased IL17 and IL23 levels, correlate with disease activity in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2009; 68(4):604-6.
48. Lin J, Yue LH, Chen WQ. Decreased Plasma IL-22 Levels and Correlations with IL-22-Producing T Helper Cells in Patients with New-Onset Systemic Lupus Erythematosus. *Scand J Immunol* 2014; 79(2):131-6.
49. Paramarta JE, Baeten D. Spondyloarthritis: from unifying concepts to improved treatment. *Rheumatology* 2013.
50. Chou CT. How to translate basic knowledge into clinical application of biologic therapy in spondyloarthritis. *Clin Dev Immunol* 2013; 2013:369202.
51. Romero-Sanchez C, Jaimes DA, Londono J, De Avila J, Castellanos JE, Bello JM, et al. Association between Th-17 cytokine profile and clinical features in patients with spondyloarthritis. *Clin Exp Rheumatol* 2011; 29(5):828-34.
52. Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. *Arthritis Rheum* 2009; 60(6):1647-56.
53. Ciccia F, Accardo-Palumbo A, Alessandro R, Rizzo A, Principe S, Peralta S, et al. Interleukin-22 and interleukin-22-producing NKp44+ natural killer cells in subclinical gut inflammation in ankylosing spondylitis. *Arthritis Rheum* 2012; 64(6):1869-78.
54. Balakrishnan C, Madnani N. Diagnosis and management of psoriatic arthritis. *Indian J Dermatol Venereol Leprol* 2013; 79 (Suppl 7):S18-24.
55. Mitra A, Raychaudhuri SK, Raychaudhuri SP. Functional role of IL-22 in psoriatic arthritis. *Arthritis Res Ther* 2012; 14(2):R65.
56. Houman MH, Bel Feki N. [Pathophysiology of Behcet's disease]. *Rev Med Interne* 2014; 35(2):90-6.
57. Aktas Cetin E, Cosan F, Cefle A, Deniz G. IL-22-secreting Th22 and IFN-gamma-secreting Th17 cells in Behcet's disease. *Mod Rheumatol* 2014.
58. Cai T, Wang Q, Zhou Q, Wang C, Hou S, Qi J, et al. Increased expression of IL-22 is associated with disease activity in Behcet's disease. *PLoS one* 2013; 8(3):e59009.
59. Na SY, Park MJ, Park S, Lee ES. Up-regulation of Th17 and related cytokines in Behcet's disease corresponding to disease activity. *Clin Exp Rheumatol* 2013; 31(3 Suppl 77):32-40.
60. Usui Y. [Expression and function of ICOS on CD4 T cells and application to therapy in patients with ocular Behcet's disease with uveitis]. *Nihon Ganka Gakkai Zasshi* 2012; 116(11):1037-45.
61. Carrion M, Juarranz Y, Martinez C, Gonzalez-Alvaro I, Pablos JL, Gutierrez-Canas I, et al. IL-22/IL-22R1 axis and S100A8/A9 alarmins in human osteoarthritic and rheumatoid arthritis synovial fibroblasts. *Rheumatology* 2013; 52(12):2177-86.