

G. AZIZI^{1,2}, R. YAZDANI³, A. MIRSHAFIEY⁴

Th22 cells in autoimmunity: a review of current knowledge

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

² Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran

³ Department of Immunology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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

KEY WORDS

Th22; IL-22; autoimmune disease; autoimmunity

Corresponding author

Abbas Mirshafiey
Department of Immunology
School of Public Health
Tehran University of Medical Sciences
Tehran -14155, Box: 6446, Iran
Fax: +98 21 88954913
E-mail: mirshafiey@tums.ac.ir

Summary

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. Th22 is obviously discrete from Th17 and Th1 subsets by production of interleukin (IL)-22 but not IL-17 or IFN- γ , and also with distinguished expression of aryl hydrocarbon receptor (AHR) as the key transcription factor. This T helper subset, by producing pro-inflammatory cytokines such as IL-22 and tumor necrosis factor- α (TNF- α), is implicated in the pathogenesis of inflammatory and autoimmune disorder. This review discusses the role of Th22 and its cytokine IL-22 in the immunopathogenesis of autoimmune disease including acute coronary syndrome, psoriasis, atopic dermatitis, rheumatoid arthritis, systemic lupus erythematosus, Behçet's disease, type 1 and 2 diabetes and immune thrombocytopenia.

Introduction

Autoimmunity is the term for the immune conditions characterized by a specific response of immune system to the body's self-tissues. Autoimmune diseases are the third largest category of illness in the industrialized world, following cardiovascular diseases and cancers. There are more than 80 types of autoimmune disorders which occur when self-immune system attacks and destroy healthy body tissue by mistake (1). Autoimmunity results from a break in self-tolerance involving humoral and/or cell-mediated immune mechanisms. The exact cause of self-tolerance breakdown is unknown, however, a variety of mechanisms have been suggested as the means by which self-tolerance is failure and autoimmunity occur. One mechanism is molecular mimicry, where a foreign antigen shares sequence or structural similarities with self-antigens. In this mechanism, some microorganisms or drugs may trigger changes that confuse the immune system. Mo-

lecular mimicry has typically been characterized on an antibody or T cell level. Accordingly, in a very general sense, with respect to the underlying mechanism, autoimmune diseases are divided into humoral and cell mediated autoimmunity (2-5). Both B and T cells can be made tolerant, however it is more important to tolerate T cells than B cells because B cells cannot make antibodies to most antigens without the help of CD4⁺ T cells. There is evidence that the classes and subclasses of cellular arms of immune system are implicated in autoimmunity. One of the main cells of immune system that is implicated in autoimmune diseases is CD4⁺ T helper (Th) cell. CD4⁺ T cells sub-divide conforming to the pattern of cytokines secretion (6). The naive CD4⁺ T 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 (7). Previously, Th1 cells were thought to be the main effector T cells responsible for the autoimmunity and inflammation. How-

ever, Th17 and Th22 cells are two emerging Th cell subsets that link the immune response to tissue inflammation and autoimmunity (8).

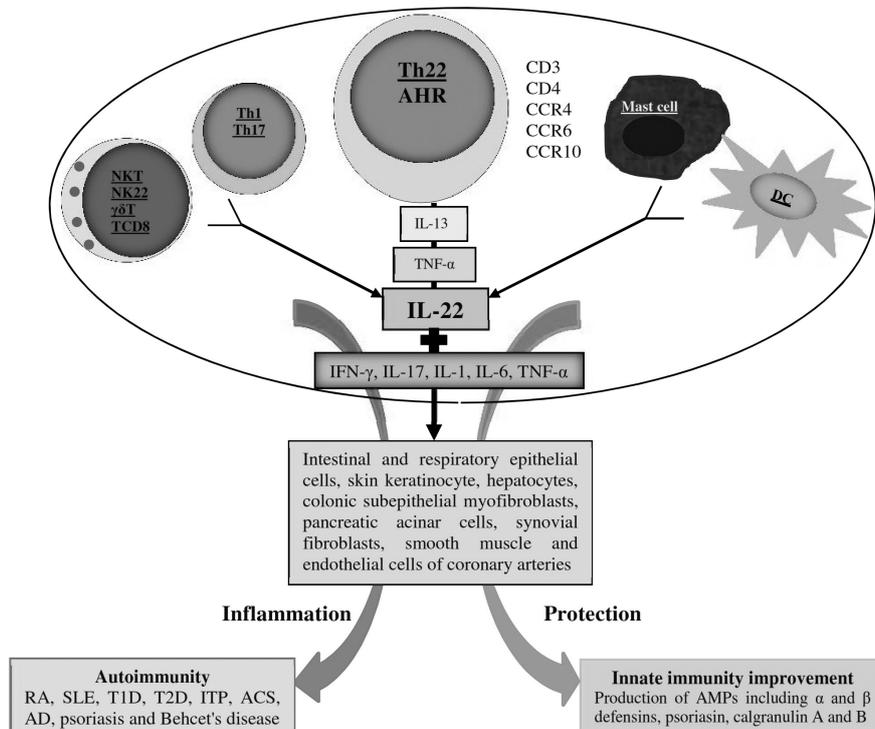
Newly identified Th22

In recent years, our knowledge of CD4⁺ T cell differentiation has mainly elevated, and to date the novel subsets continue to be identified (9). Th22 is described by Trifari et al. in 2009 and identified by secretion of various cytokines such as IL-13, tumor necrosis factor- α (TNF- α) and the most important IL-22. On the other hand, Th22 cells could express chemokine receptor CCR4, CCR6, CCR10, and fibroblast growth factor isoforms (10). In addition, Th22 cells do not express IL-17, IL-23R, CCL20, CD161 (as Th17 markers), interferon gamma (IFN- γ) (as Th1 marker) and IL-4 (as Th2 marker) (11). Th22 cells do not express T-bet (Th1-associated transcription), GATA-3 (Th2-associated transcription) and retinoic acid-related orphan receptor (ROR) γ t (Th17-associated transcription) (12). Fur-

thermore, Duhon et al. have noticed which Th22 cells expressed these transcription factors very low or undetectable (12). It has been discovered that a distinct transcription factor called the aryl hydrocarbon receptor (AHR) mediated development of Th22 cells (13).

In addition, on study showed which stimulated AHR could contribute to production of IL-22 by notch signaling. In other words, notch-associated activation of CD4⁺ T cells result in elevation of IL-22 secretion even without induction of signal transducer and activator of transcription 3 (STAT3) (14). Indeed, these data indicate which Th22 cells are as a distinct lineage from the Th17, Th1 and Th2 subtypes (15, 16). It has been discovered which IL-6 and TNF- α could differentiate naive CD4⁺ T cells to Th22 cells, and on the other hand, this differentiation could be prevented by elevating concentrations of TGF- β (17). In addition, it has been reported which of conventional dendritic cells (DCs) and/or plasmacytoid DCs might lead to differentiation of naive CD4⁺ T cells to Th22 cells. By using activated conventional DCs and plasmacytoid DCs, Trifari et al. have revealed

Figure 1 - The mechanisms of action of IL22. IL-22 produced by innate and adaptive immune cells especially Th22 is beneficial to the host defense in many infectious diseases. Moreover, depending on the target tissue, IL-22 could also be pathogenic in autoimmune disorder 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. AMPs; anti-microbial peptides, RA; rheumatoid arthritis, SLE; systemic lupus erythematosus, ACS; acute coronary syndrome, AD; atopic dermatitis, T1D; type 1 diabetes, T2D; type 2 diabetes, ITP; immune thrombocytopenia.



that human DCs actually induce the development of Th22 cells from naive CD4⁺T cells. Comparatively, plasmacytoid DCs by producing TNF- α and IL-6 are stronger than conventional DCs in the development of Th22 cells (10). IL-22 receptor is not expressed in cells of immune system. Thus, although IL-22 secreted by Th22 does not serve the communication between immune cells, however IL-22 is as a Th22 cell mediator which directly increase the innate, nonspecific immunity on epithelial and stromal cells including intestinal and respiratory epithelial cells, skin keratinocyte, hepatocytes, colonic subepithelial myofibroblasts, pancreatic acinar cells, and synovial fibroblasts derived from patients with rheumatoid arthritis (12, 18). On the one hand, Th22 and IL-22 play vital role against several infectious diseases, on the other hand, it might be pathogenic because of its inherent pro-inflammatory features; it would further elevated when IL-22 is produced together with other pro-inflammatory cytokines, in particular IL-17 (Figure 1) (19). In recent years, multiple studies have demonstrated role of Th22 in many inflammatory and autoimmune disorders such as psoriasis (20), atopic dermatitis (21), rheumatoid arthritis (22), systemic lupus erythematosus (23), acute coronary syndrome (24), Behcet's disease (25), ankylosing spondylitis (22), type 1 and 2 diabetes (26, 27), and immune thrombocytopenia (28).

The role of Th22 in autoimmune disorder

Acute coronary syndrome

Acute coronary syndrome (ACS) refers to any group of symptoms attributed to obstruction of the coronary arteries. Recent evidence has indicated that atherosclerosis is a chronic inflammatory disease with macrophages and T cells playing a critical role (29). CD4⁺ T cells play main roles in the inflammatory process of atherosclerosis and also in the onset of ACS including unstable angina pectoris and acute myocardial infarction (30). It is demonstrated that ACS occurs as a consequence of coronary plaque rupture or plaque erosion, and changes in the functions of CD4⁺T cells, especially Th cells, were found in patients with ACS (31). Among T cells, Th1 are recognized as having a pro-atherogenic role. In addition, Th17 and Th9 have been identified in atherosclerotic lesions. They have been linked to atheroma development by production of pro-inflammatory cytokines present in these lesions (24). Recently, Th22 have been identified in the atheromatous environment, and their presence and function has been investigated (32). Huang et al. suggest that Th22 cell is a gradually proved potential biomarker for ACS. In a study, Oliveira et al. showed the presence of Th17, Th2, and Th22 in human carotid lesions and indicate that interactions among them may contribute to the atheroma progression and destabilization (33). In another research, Lin et al.

in 2013 indicate that AHR expression, peripheral Th22 number and their effector cytokine IL-22 levels were obviously increased in patients with acute myocardial infarction, stable and unstable angina pectoris compared with patients without coronary artery disease, indicating that peripheral Th22 cells played major roles at the ACS (32). Interestingly, similar data was evident by Zhang et al., which demonstrated that the Th22, Th17 and Th17/Th1 cells were considerably higher in acute myocardial infarction and unstable angina pectoris patients than those of stable angina patients and healthy control (34). In an experimental model Hanawa et al. reported that IL-22 could interact with fibroblasts, smooth muscle cells, and endothelial cells in the rat experimental autoimmune myocarditis (35). Moreover, there was a positive correlation between the frequency of Th22 cells and IL-22 concentration in acute myocardial infarction and unstable angina pectoris patients (34). In a study, Xia et al. showed that Th22 cells played pivotal roles in coronary plaque rupture or plaque erosion, since IL-22 was detected in the carotid plaque (36). These findings confirmed increased frequencies of IL-22, Th22 and Th17 cells in ACS patients, which showed that Th22 and Th17 cells may play a potential role in plaque destabilization and the development of ACS (34).

Psoriasis

Psoriasis is a common chronic inflammatory disorder which is identified by red scaly skin plaques with hyperproliferative of keratinocytes. Epidermal hyperplasia and infiltration of inflammatory cells into skin lesions are major histological results in patients with psoriasis (37, 38). A key event in psoriasis is migration of immune cells from the dermis into the epidermis, where they induce keratinocytes proliferation (38). Although pathogenesis of psoriasis is unknown, however it has been identified which several immune cells including DCs, CD4⁺ T cell subsets (Th17, Th22, and Th1 cells), CD8⁺ T cells and neutrophils exist in psoriatic skin lesions and might involve in etiology of psoriasis disorder (38). IL-17 and IL-22 are synthesized by Th17, Th22, and Th1 in psoriatic skin lesions (38). It has supposed that Th1 is principally correlated with the pathogenesis of psoriasis, but Kagami et al. suggested which Th17 cells trough secretion of IL-17 and IL-22 are more implicated. They also reported which there was an augmentation of Th22 and Th1 cells in psoriatic patients, but to a lesser degree (38). Conversely, Fujita et al. suggested that the majority of IL-22-producing CD4⁺ T cells are neither Th17, Th1, and nor Th2 however; they did not study the majority of Th22 in psoriasis. Indeed, psoriasis skin lesions contain a population of T cells that co-synthesize IL-17 and IL-22, but the majority of IL-22-producing T cells is neither Th17, Th1, and nor Th2, and may represent a unique subset of IL-22-producing helper T cells, Th22 (39). Eyerich et al. have reported that although Th22 similar to Th17 are scarcely detected

in PBMCs, but Th22 cells are largely founded in T-cell population isolated from the skin of psoriasis patients (15). Moreover, it has been discovered which Th22 clones derived from psoriatic patients are constant in vitro and demonstrate a transcriptome profile apparently different from Th1, Th2, and Th17 cells. Therefore, one supposes that genes encoding proteins including Fibroblast growth factors (FGFs) and chemokines might contribute to angiogenesis and fibrosis. It has been noticed that when primary human keratinocytes cultured with Th22 supernatants, it led to expression of transcriptome response profile which comprised genes involved in adaptive and innate immunity through activation of T cell and NK promoting factors including IL-15 and IL-7, in keratinocytes. In addition, IL-32 (as a TNF- α -enhancing cytokine) is produced by keratinocytes and result in production of TNF- α from Th22 cells, which might activate pro-inflammatory Th22 responses. Then, there is a synergic dependency between the pro-inflammatory responses of Th22 and IL-22 and TNF- α (15, 40). Conversely, it has been shown an elevated wound healing in an in vitro injury model Th22 supernatants that exclusively related to IL-22 (15). It is suggested, IL-22 alone could play an important role in expression of multiple genes which contribute to tissue repairing and wound healing including kallikerin subgroup of serine proteases and serpin family of protease inhibitors (41, 42).

Atopic dermatitis

Atopic dermatitis as a chronic inflammatory skin disease identified by episodes of acute eczema alternating and cutaneous hyperreactivity to environmental triggers and often is seen in patients with personal or family history of asthma and allergic rhinitis (43, 44). It is considered that expansion of atopic dermatitis belongs to disease-specific and time-dependent recruitment of various leukocytes could influencing resident skin cells by cytotoxic mechanisms (45). It is supposed in the past which Th2 cells are responsible for atopic dermatitis diseases, but nowadays Th17 and Th22 cells have considered which involve in development of atopic dermatitis disease (45, 46). Indeed, Th17 and Th22 cells specifically involve in dialogue with non-immune cells. In this case, role of Th17 and Th22 cells in multiple immune-associated skin disorder including psoriasis, atopic dermatitis, and allergic contact dermatitis are defined (45). Koga et al. have demonstrated an elevation of percentage of Th17 cells in peripheral blood of patients with atopic dermatitis which has correlated with severity of disease (47). In contrast, Nograles et al. have founded an elevation of production of IL-22 from T22 cells in lesional skin of patients with atopic dermatitis. They also have noticed a significant increase in population of Th1 and Th17 cells in psoriatic skin in comparison with atopic dermatitis, while population of Th2 and Th22 were strongly increased in atopic dermatitis (46). Furthermore, Nograles et

al have reported a significant augmentation of IL-22-producing T-cell cells in atopic dermatitis patients compared with psoriasis. In this study, they have seen an extreme number of CD4⁺ and CD8⁺ cells which could uniquely produce IL-22. Indeed, these cells were responsible for almost 70% of the IL-22 secretion in atopic dermatitis disease, with low frequencies of Th1, Th2, and Th17 T-cells that co-secrete IL-22 (46). Overall, these data indicate that the new subsets of IL-22 producing Th22 and Tc22 T cells could involve in elevated expression of IL-22 in chronic atopic dermatitis skin, and contribute to Th2/T22 immune polarization in patients with chronic atopic dermatitis.

Rheumatoid arthritis

RA is considered as a chronic inflammatory disease that identified by the reposition and proliferation of inflammatory cells in the synovial (joint) space. According to RA is a chronic disease, inflammation of several joints leads to damage of the joint cartilage and ablation of bone. Pathogenesis of RA is unclear yet, however it is observed the activation of multiple cells such as T cells, B cells, macrophages, mast cells, and fibroblast-like synoviocytes (FLSs) which involve in synovial inflammation and joint destruction (48). CD4⁺ T helper cells contribute to the development and progression of RA. Among CD4⁺ T helper cells, recognition of Th17 cells resulted in better understanding of pathogenesis of RA (48). Although it recently has been demonstrated Th22 cells involve in the pathogenesis of RA, however its role in the pathophysiology of RA still has remained undefined. For the first time, Zhang L et al. has been identified which augmentation of Th22 cells could associated with Th17 cells in RA patients. They have been demonstrated that Th22 and Th17 cells as well as IL-22 were significantly increased in RA patients in comparison with osteoarthritis and healthy individuals; however it has not observed significant difference regarding Th1 cells and IL-17. Furthermore, this study has been reported a positive correlation regarding Th22 cells with IL-22 and Th17 cells in patients with RA (49). Later, another study evaluated frequencies of Th22 cells, Th17 cells and Th1 cells in both RA patients and ankylosing spondylitis. Again, it has been reported elevation of Th22 cells, Th17 cells and IL-22 in patients with RA and ankylosing spondylitis in comparison with osteoarthritis patients and healthy individuals. Furthermore, consistent with previous study, it has been reported Th22 has a positive correlation with Th17 cells and IL-22. However, although it has shown that the frequency of Th22 and Th17 cells were positively correlated with disease activity in RA patients, but this correlation has not seen in ankylosing spondylitis patients (22). Van Hamburg et al. have demonstrated elevation of Th17 and Th22 cell populations in patients with RA similar to previous studies, which were existed in RA synovial fluid. Moreover, they have founded that Th17 were more potent to

stimulate synovial fibroblasts (RASf) in production of IL-6, IL-8, MMP-1 and MMP-3 compared with Th22 cells. These data uncover which formation of synovial inflammation by IL-17A/Th17 cell is independent of Th22 cells and IL-22 (50). However, Zhao et al. have founded which percentages of Th22 cells in RA patients correlated positively with the levels of plasma IL-22 (51), but a positive correlation between plasma IL-22 and Th17 cells were seen only in ankylosing spondylitis patients not in RA patients (22).

Psoriatic arthritis

Psoriatic arthritis is a joint disease characterized by both psoriasis and a related form of inflammatory arthritis (52). Increased frequencies of Th17 and Th22 cells along with their pro-inflammatory cytokine network, including TNF- α , IL-17, and IL-22, are the feature of both skin lesions (plaques) in psoriasis and synovium in 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 and joint role as well as divergent roles in the pathogenesis of psoriasis and psoriatic arthritis. Benham et al. demonstrate 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 (53, 54). In patients with psoriatic arthritis, Th17 cells number 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 as frequency of Th22 cell 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 (53).

Diabetes

Among autoimmune diseases, type 1 diabetes (T1D), also named autoimmune diabetes, have afflicted 10 million peoples worldwide. This disease is caused by autoimmunity-mediated destruction of pancreatic-cells, leading to insulin deficiency, hyperglycemia and complications. Many components of the immune system are implicated in autoimmunity leading to β cell destruction, including cytotoxic and helper T-cells, B-cells, macrophages, and DCs (55). Cytokines produced by these cells have also been shown to play a key role in β cell destruction

and regulation of autoimmunity in T1D. The inflammatory process in early diabetes is thought to be initiated and propagated by the effect of Th1-secreted cytokines e.g. IFN- γ (55). It is showed that levels of IL-6 and TNF- α may be useful in the prediction of proliferative diabetic retinopathy, whereas higher IL-10 levels are related to lower risk of diabetic retinopathy in diabetes patients (56). Dalmas et al. showed a pronounced pro-inflammatory signature of adipose tissue macrophages in type 2 diabetic (T2D) obese patients, frequently driven by increased NLRP3-dependent IL-1 β production. It is revealed that IL-22 increased IL-1 β release by inducing pro-IL-1 β transcription via activation of C-Jun pathways in macrophages. These findings identified IL-1 β and IL-22 as main players in adipose tissue inflammation, with a pathological relevance to obesity-induced T2D (57). However, Chenet al. found that the mean IL-22 serum levels were somewhat lower in diabetic patients than in normal controls (58). It is known that IL-22 can up-regulate Regenerating (Reg) genes expression in islets and could potentially induce regeneration of β cells and inhibit their apoptosis. Finally, cytokines both induce and regulate inflammatory condition and have the potential to regenerate and preserve insulin-producing β cells in the islets (59). In a study by Xu et al. Th17 and Th22 were significantly elevated in patients with T1D compared to control donor, while there were no significant differences in Th1 cells. Also, Th22 cells showed a positive correlation with Th17 cells in these patients. However, there was not any correlation between IL-17 and IL-22 in sera. Therefore, these findings showed that Th22 may contribute to the pathogenesis of T1D (27).

The systemic chronic inflammation has been postulated to bridge the increased risk of cardiovascular disease and T2D. In newest study Zhao et al. suggest that both peripheral frequencies and total numbers of Th1, Th17, and Th22 cells were further increased in diabetic patients with coronary atherosclerotic heart disease. Further analysis confirmed that increased pro-inflammatory Th cells, especially Th22, were independent risk factors of cardiovascular complication in diabetes. Furthermore, Th1 and Th22 frequency demonstrated considerable potential in predicting coronary atherosclerotic heart disease in diabetes (60). In another study Zhao et al. showed an increased Th22 frequencies and IL-22 concentrations in obesity and T2D (26). Some data indicate a conceivable role of Th22 cells in diabetic retinopathy. Although, Chenet al. suggested that IL-22 serum levels were slightly lower in diabetic patients than in normal controls but the IL-22 level of PBMCs was clearly elevate in patients with proliferative diabetic retinopathy compared with the level in patients with non-proliferative diabetic retinopathy and healthy controls (58). Finally, the significant correlation of mentioned data implied that Th22 might play a more important role in both insulin resistance and β -cell impairment.

Behçet's disease

Behçet's disease (BD) as a recurrent systemic inflammatory disease is identified by oral and genital mucous ulcer, intraocular inflammation (uveitis) and skin lesions (61). It has been reported which diminution of Tregs cells and increase in population of Th1 and Th22 cells as well as Th17/Th1 cells could involve in pathogenesis of BD (62). Aktas et al. have uncover which population of Th1 and Th22 cells have strongly elevated, and percentage of Treg cells have dramatically decreased in patients with Behçet. Moreover, they have shown which the frequency of recurrent oral ulcers was associated with elevation of Th22 cells in patients with Behçet (62). IL-22 (as a major cytokine of Th22) is correlated with disease activity as well as presence of small vessel inflammation in Behçet's disorder which could clarify the role of IL-22 in pathogenesis of this disease (63). It has been founded that uveitis is major reason of vision loss in BD which manifested due to recurrent ocular inflammatory attacks (64). It is supposed that IL-22 producing CD4⁺ T cells trough reaction with self-antigens might involve in pathogenesis of uveitis (25). Cai et al. have recognized an increase in expression level of IL-22 in supernatants of stimulated PBMCs and CD4⁺T cells of BD with active uveitis compared with BD without active uveitis and healthy individuals. Furthermore, they have identified an elevation of IL-22-producing CD4⁺T cells population in BD patients with active uveitis (63). Sugita et al. have confirmed above data and founded Th22 clones from ocular samples taken from BD secreted high amounts of IL-22 and TNF- α cytokines, but not IFN- γ and IL-17. Also, they have demonstrated which CD4⁺ T cells related to BD patients in the presence of IL-6 and TNF- α in vitro could differentiated into Th22 cells and polarized Th22 cell could secrete a large amount of IL-22. In addition, IL-22-producing T cells in the presence of retinal antigens could produce high level of IL-22 in mice with experimental autoimmune uveitis. These data indicate which IL-22 and TNF- α producing Th22 cells probably involve in ocular immune response in BD patients (25).

Immune thrombocytopenia

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low count platelet due to decreased platelet production as well as increased platelet destruction by autoimmune mechanisms in which the patient's immune system reacts with a platelet of autoantigens. In ITP a shift toward B cells producing autoantibodies together with CD4⁺ T helper cells has been reported. Cao et al. suggested that the plasma IL-22 levels in ITP patients were significantly higher than that in healthy controls, and this elevation was correlated with Th1 and Th22 cells in these patients (65). In addition, it is shown that the percentages of both Th1 and Th22 cells in ITP patients elevated as

compared to healthy controls. Whereas, the percentage of Th17 cells was not significantly different between ITP patients and control groups, and there was no statistical correlation between the IL-22 level and the percentage of Th17 cells in active ITP patients. Therefore, the elevated IL-22 level correlates to Th1 and Th22 cells percentage, which may play a synergistic effect in the immunopathogenesis of ITP, while Th17 cells may not be correlated with the occurrence of active ITP (66). In contrast, Wu et al. in their recent study showed that the proportion of peripheral blood Th1, Th17, Th22 cell subgroups and the levels of IFN- γ , IL-17, IL-22 in culture supernatant increased in chronic ITP patients (67). In another study by Hu et al. Th22 cells showed a positive correlation with the levels of plasma IL-22 as well as Th17 and Th1 cells in ITP patients. Additionally, the proportion of Th22 cells was higher in autoantibody-negative ITP patients than in autoantibody-positive patients (68). To investigate the change of Th22 cells in the peripheral blood of the primary ITP patients and evaluate the significance of Th22 cells in ITP, Liu et al. used the peripheral blood of ITP before and after therapy, in ITP patients. The results indicate that proportion of Th22 cells and the levels of cytokine IL-22, IL-6, TNF- α , and IL-22 mRNA in patients before and after therapy were significantly higher than those in healthy group. Briefly, in ITP patients, the number of Th22 cells and the levels of TNF- α and IL-6 increase, whereas the level of TGF- β decreases (28). In a clinical trial, Cao et al. evaluated the effects of dexamethasone on regulating IL-22 production and correcting Th1 and Th22 polarization in ITP. In this study plasma IL-22 concentration and the proportion of Th1 and Th22 cells were significantly increased in pretherapy patients compared to healthy controls, whereas, high-dose dexamethasone administration reduced IL-22 production and also corrected the imbalance between Th1 and Th22 subsets. They concluded that IL-22 levels were positively associated with Th1 and Th22 cells in ITP patients before and after dexamethasone therapy (69).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that identified by acute and chronic inflammation of several tissues such as skin, kidneys, joints, brain, and other organs. Several abnormalities in activated immune system of patients with SLE including secretion of autoantibodies, defective elimination of autoantibodies, complement and cytokine activation, accumulation of immune-complex in tissue involve in tissue and organ damages. Hence, defective immune tolerance against self-antigens as well as extensive T cells and B cells activation contribute to development of SLE (70). IL-17 and IL-22 which are mainly secreted by Th17 and Th22 cells respectively, could clarify progress and induction of autoimmune phenomena (71, 72). Zhao et al. have recognized which

the population of Th1, Th17 and Th22 cells as well plasma IL-22 and IL-17A were strongly increased in patients with SLE in comparison with control individuals. They also evaluated the frequency of Th22 and Th17 cells in these patients and founded which although there is a positive correlation between Th22 and Th17 cells, however this correlation was not seen with the other inflammatory values including CRP, ERS and C3 in SLE patients. These data regarding Th17 and Th22 may shed a new light into the way toward the better understanding of role these cells in pathogenesis of SLE disorder (72). In recent years, role of Th22 cells and IL-22 in pathogenesis of SLE have been more identified. In one study, it has been noticed which reduced IL-22 levels, but not elevated IL-17 and IL-23 levels, were associated with disease activity in SLE patients (73). However, Yang et al. offered which although Th17 could associate with activity of SLE, however Th22 but not Th17 might consider as a good index to predict the tissue involvement of SLE. The major results is concentrated on elevation of Th22 cells and serum IL-22 levels in patients with sole lupus skin disease and reduction of Th22 cells and serum IL-22 levels in patients with sole lupus nephritis. Moreover, it has been discovered a positive correlation between Th22 cells but not Th1 and Th17 cells with IL-22 secretion and plasma IL-22 levels (23, 74). In a novel study by Lin et al. founded which correlation between plasma IL-22 levels and Th22 cells could different features in new-onset of patients with SLE than relapsing SLE patients. It has been noticed that there was a significant reduction of the IL-22 levels in new-onset SLE patients in comparison with relapsing SLE patients and healthy individuals (74).

Conclusion

In autoimmunity, one of the most important players is the CD4 T cell. The CD4 T cell lineage consists of a number of phenotypically and functionally distinct subsets. Recently, Th22 cells were identified as a Th cells 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 the immunopathogenesis of autoimmune diseases; therefore, therapeutical approach based on the pharmacological signalling disruption of IL-22 could be useful for the treatment of these types of diseases (75). Treatment with recombinant cytokine or gene therapy for IL-22 may reduce tissue destruction during inflammatory responses. It is demonstrated that in the presence of anti-TNF- α - and anti-IL-6-blocking antibody, Th22 cells failed to produce IL-22. In addition, infliximab-pretreated Th22 cells produced less IL-22 and TNF- α (25). In a study, Mitra et al. demonstrated successful inhibition of IL-22 induced fibroblast like synoviocytes proliferation by anti-IL-22R antibody with blocking of IL-22/IL-22R interaction, which may be considered as a novel thera-

peutic target for psoriatic arthritis (54). 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 entirely reflect Th22 function, since IL-22 apart from Th22 cells is also expressed by other cells. Hence, targeting Th22 or IL-22 is nonselective and may affect all of the Th22 and IL-22 in the whole body, leading adverse 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 (75). Therefore, further studies are required for clarifying the accurate role of Th22 and IL-22 in autoimmunity.

References

1. Chang CL, Chen YC, Chen HM, Yang NS, Yang WC. Natural cures for type 1 diabetes: a review of phytochemicals, biological actions, and clinical potential. *Current medicinal chemistry*. 2013;20(7):899-907. PubMed PMID: 23210779.
2. Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. *Clinical reviews in allergy & immunology*. 2012;42(1):102-11. PubMed PMID: 22095454. Pubmed Central PMCID: 3266166.
3. Gillissen G, Pusztai-Markos Z. Cell mediated immune regulation in autoimmunity. *Allergologia et immunopathologia*. 1979;7(2):153-68. PubMed PMID: 313696.
4. Blank M, Shoenfeld Y. B cell targeted therapy in autoimmunity. *Journal of autoimmunity*. 2007;28(2-3):62-8. PubMed PMID: 17391915.
5. Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. *Annual review of immunology*. 2006;24:467-96. PubMed PMID: 16551256.
6. Townsend MJ, McKenzie AN. Unravelling the net ? cytokines and diseases. *Journal of cell science*. 2000;113(Pt 20):3549-50. PubMed PMID: 11017869.
7. Gutter I, Becher B. APC-derived cytokines and T cell polarization in autoimmune inflammation. *The Journal of clinical investigation*. 2007;117(5):1119-27. PubMed PMID: 17476341. Pubmed Central PMCID: 1857272.
8. Akdis M, Palomares O, van de Veen W, van Splunter M, Akdis CA. TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection. *The Journal of allergy and clinical immunology*. 2012;129(6):1438-49; quiz50-1. PubMed PMID: 22657405.
9. Li H, Rostami A. IL-9: basic biology, signaling pathways in CD4+ T cells and implications for autoimmunity. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology*. 2010;5(2):198-209. PubMed PMID: 20020328.
10. 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. *Nature immunology*. 2009;10(8):864-71. PubMed PMID: 19578368.
11. Larsen M, Arnaud L, Hie M, Parizot C, Dorgham K, Shoukry M, et al. Multiparameter grouping delineates heterogeneous pop-

- ulations of human IL-17 and/or IL-22 T-cell producers that share antigen specificities with other T-cell subsets. *European journal of immunology*. 2011;41(9):2596-605. PubMed PMID: 21688259.
12. 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. *Nature immunology*. 2009;10(8):857-63. PubMed PMID: 19578369.
 13. 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(+) T cells to promote the development of IL-22-secreting Th cells. *Human immunology*. 2012;73(8):795-800. PubMed PMID: 22609446.
 14. 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. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(13):5943-8. PubMed PMID: 20231432. Pubmed Central PMCID: 2851859.
 15. 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. *The Journal of clinical investigation*. 2009;119(12):3573-85. PubMed PMID: 19920355. Pubmed Central PMCID: 2786807.
 16. 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 research & therapy*. 2011;13(5):R166. PubMed PMID: 21996293. Pubmed Central PMCID: 3308100.
 17. 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 / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology*. 2013;21(4):857-60. PubMed PMID: 23998574.
 18. 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. PubMed PMID: 15308104.
 19. Rutz S, Eidsencken C, Ouyang W. IL-22, not simply a Th17 cytokine. *Immunological reviews*. 2013;252(1):116-32. PubMed PMID: 23405899.
 20. Cheuk S, Wiken M, Blomqvist L, Nylen S, Talme T, Stahle M, et al. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. *Journal of immunology*. 2014;192(7):3111-20. PubMed PMID: 24610014. Pubmed Central PMCID: 3962894.
 21. Souwer Y, Szegedi K, Kapsenberg ML, de Jong EC. IL-17 and IL-22 in atopic allergic disease. *Current opinion in immunology*. 2010;22(6):821-6. PubMed PMID: 21087848.
 22. 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. PubMed PMID: 22485125. Pubmed Central PMCID: 3317658.
 23. 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. *Journal of clinical immunology*. 2013;33(4):767-74. PubMed PMID: 23435610.
 24. Huang Y, Xu T, Li J. Th22 cell is a gradually proved potential biomarker for acute coronary syndrome. *Mediators of inflammation*. 2014;2014:813926. PubMed PMID: 24895489. Pubmed Central PMCID: 4034660.
 25. 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. *Journal of immunology*. 2013;190(11):5799-808. PubMed PMID: 23630362. Pubmed Central PMCID: 3659956.
 26. Zhao R, Tang D, Yi S, Li W, Wu C, Lu Y, et al. Elevated peripheral frequencies of Th22 cells: a novel potent participant in obesity and type 2 diabetes. *PloS one*. 2014;9(1):e85770. PubMed PMID: 24465695. Pubmed Central PMCID: 3894984.
 27. Xu X, Zheng S, Yang F, Shi Y, Gu Y, Chen H, et al. Increased Th22 cells are independently associated with Th17 cells in type 1 diabetes. *Endocrine*. 2014;46(1):90-8. PubMed PMID: 23928796.
 28. Liu LM, Zhang XX, Zhao GS, Si YJ, Lin GQ, Zhang YM, et al. [Change of Th22 cells in peripheral blood of patients with primary immune thrombocytopenia and clinical implication]. *Xi bao yu fen zi mian yi xue za zhi = Chinese journal of cellular and molecular immunology*. 2012;28(12):1314-6. PubMed PMID: 23232525.
 29. Matusik P, Guzik B, Weber C, Guzik TJ. Do we know enough about the immune pathogenesis of acute coronary syndromes to improve clinical practice? *Thrombosis and haemostasis*. 2012;108(3):443-56. PubMed PMID: 22872109.
 30. Weyand CM, Goronzy JJ, Liuzzo G, Kopecky SL, Holmes DR, Jr., Frye RL. T-cell immunity in acute coronary syndromes. *Mayo Clinic proceedings*. 2001;76(10):1011-20. PubMed PMID: 11605685.
 31. Methe H, Brunner S, Wiegand D, Nabauer M, Koglin J, Edelman ER. Enhanced T-helper-1 lymphocyte activation patterns in acute coronary syndromes. *Journal of the American College of Cardiology*. 2005;45(12):1939-45. PubMed PMID: 15963390.
 32. Lin YZ, Wu BW, Lu ZD, Huang Y, Shi Y, Liu H, et al. Circulating Th22 and Th9 levels in patients with acute coronary syndrome. *Mediators of inflammation*. 2013;2013:635672. PubMed PMID: 24453425. Pubmed Central PMCID: 3884785.
 33. Oliveira RT, Silva RM, Teo FH, Mineiro MF, Ferreira MC, Altemani A, et al. Detection of TCD4+ subsets in human carotid atheroma. *Cytokine*. 2013;62(1):131-40. PubMed PMID: 23474106.
 34. Zhang L, Wang T, Wang XQ, Du RZ, Zhang KN, Liu XG, et al. Elevated frequencies of circulating Th22 cell in addition to Th17 cell and Th17/Th1 cell in patients with acute coronary syndrome. *PloS one*. 2013;8(12):e71466. PubMed PMID: 24312440. Pubmed Central PMCID: 3849482.
 35. Chang H, Hanawa H, Liu H, Yoshida T, Hayashi M, Watanabe R, et al. Hydrodynamic-based delivery of an interleukin-22-Ig fusion gene ameliorates experimental autoimmune myocarditis in rats. *Journal of immunology*. 2006;177(6):3635-43. PubMed PMID: 16951323.
 36. Xia Q, Xiang X, Patel S, Puranik R, Xie Q, Bao S. Characterisation of IL-22 and interferon-gamma-inducible chemokines in human carotid plaque. *International journal of cardiology*. 2012;154(2):187-9. PubMed PMID: 22104996.
 37. Nograles KE, Davidovici B, Krueger JG. New insights in the immunologic basis of psoriasis. *Seminars in cutaneous medicine and surgery*. 2010;29(1):3-9. PubMed PMID: 20430301. Pubmed Central PMCID: 2868373.
 38. Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. *The Journal of investigative dermatology*. 2010;130(5):1373-83. PubMed PMID: 20032993. Pubmed Central PMCID: 2892169.

39. Fujita H, Nograla KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG. Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106(51):21795-800. PubMed PMID: 19996179. Pubmed Central PMCID: 2799849.
40. Albanesi C, Scarponi C, Cavani A, Federici M, Nasorri F, Girolomoni G. Interleukin-17 is produced by both Th1 and Th2 lymphocytes, and modulates interferon-gamma- and interleukin-4-induced activation of human keratinocytes. *The Journal of investigative dermatology*. 2000;115(1):81-7. PubMed PMID: 10886512.
41. Ouyang W. Distinct roles of IL-22 in human psoriasis and inflammatory bowel disease. *Cytokine & growth factor reviews*. 2010;21(6):435-41. PubMed PMID: 21106435.
42. Tian T, Yu S, Ma D. Th22 and related cytokines in inflammatory and autoimmune diseases. *Expert opinion on therapeutic targets*. 2013;17(2):113-25. PubMed PMID: 23256771.
43. Aubert H, Bernier C, Debons M, Chavigny JM, Barbarot S, Stalder JF [Atopic dermatitis of the child]. *La Revue du praticien*. 2013;63(9):1271-81.
44. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *Journal of Clinical Investigation*. 2004;113(5):651.
45. Cavani A, Pennino D, Eyerich K. Th17 and Th22 in skin allergy. *Chemical immunology and allergy*. 2012;96:39-44. PubMed PMID: 22433369.
46. Nograla KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing "T22" T cells account for up-regulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *The Journal of allergy and clinical immunology*. 2009;123(6):1244-52 e2. PubMed PMID: 19439349. Pubmed Central PMCID: 2874584.
47. Koga C, Kabashima K, Shiraiishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. *The Journal of investigative dermatology*. 2008;128(11):2625-30. PubMed PMID: 18432274.
48. Azizi G, Jadidi-Niaragh F, Mirshafiey A. Th17 Cells in Immunopathogenesis and treatment of rheumatoid arthritis. *International journal of rheumatic diseases*. 2013;16(3):243-53. PubMed PMID: 23981743.
49. 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. *Journal of clinical immunology*. 2011;31(4):606-14. PubMed PMID: 21556937.
50. 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. *Annals of the rheumatic diseases*. 2013;72(10):1700-7. PubMed PMID: 23328939.
51. Zhao L, Jiang Z, Jiang Y, Ma N, Zhang Y, Feng L, et al. IL-22+ CD4+ T cells in patients with rheumatoid arthritis. *International journal of rheumatic diseases*. 2013;16(5):518-26. PubMed PMID: 24164838.
52. Balakrishnan C, Madhani N. Diagnosis and management of psoriatic arthritis. *Indian journal of dermatology, venereology and leprology*. 2013;79 Suppl 7:S18-24. PubMed PMID: 23974691.
53. Benham H, Norris P, Goodall J, Wechalekar MD, FitzGerald O, Szentpetery A, et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. *Arthritis research & therapy*. 2013;15(5):R136. PubMed PMID: 24286492.
54. Mitra A, Raychaudhuri SK, Raychaudhuri SP. Functional role of IL-22 in psoriatic arthritis. *Arthritis research & therapy*. 2012;14(2):R65. PubMed PMID: 22417743. Pubmed Central PMCID: 3446433.
55. Hassan GA, Sliem HA, Ellethy AT, Salama Mel S. Role of immune system modulation in prevention of type 1 diabetes mellitus. *Indian journal of endocrinology and metabolism*. 2012;16(6):904-9. PubMed PMID: 23226634. Pubmed Central PMCID: 3510959.
56. Lee JH, Lee W, Kwon OH, Kim JH, Kwon OW, Kim KH, et al. Cytokine profile of peripheral blood in type 2 diabetes mellitus patients with diabetic retinopathy. *Annals of clinical and laboratory science*. 2008;38(4):361-7. PubMed PMID: 18988929.
57. Dalmás E, Ventecléf N, Caer C, Poitou C, Cremer I, Aron-Wisnewsky J, et al. T cell-derived IL-22 amplifies IL-1beta-driven inflammation in human adipose tissue: relevance to obesity and type 2 diabetes. *Diabetes*. 2014;63(6):1966-77. PubMed PMID: 24520123.
58. Chen H, Wen F, Zhang X, Su SB. Expression of T-helper-associated cytokines in patients with type 2 diabetes mellitus with retinopathy. *Molecular vision*. 2012;18:219-26. PubMed PMID: 22312190. Pubmed Central PMCID: 3272054.
59. Singh B, Nikoipour E, Huszarik K, Elliott JF, Jevnikar AM. Immunomodulation and regeneration of islet Beta cells by cytokines in autoimmune type 1 diabetes. *Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research*. 2011;31(10):711-9. PubMed PMID: 21851268.
60. Zhao RX, Li WJ, Lu YR, Qin J, Wu CL, Tian M, et al. Increased peripheral proinflammatory T helper subsets contribute to cardiovascular complications in diabetic patients. *Mediators of inflammation*. 2014;2014:596967. PubMed PMID: 24803740. Pubmed Central PMCID: 3997161.
61. Houman MH, Bel Feki N. [Pathophysiology of Behcet's disease]. *La Revue de medecine interne / fondee par la Societe nationale francaise de medecine interne*. 2014;35(2):90-6. PubMed PMID: 24210264. *Physiopathologie de la maladie de Behcet*.
62. Aktas Cetin E, Cosan F, Cefle A, Deniz G. IL-22-secreting Th22 and IFN-gamma-secreting Th17 cells in Behcet's disease. *Modern rheumatology / the Japan Rheumatism Association*. 2014 Feb 5. PubMed PMID: 24498963.
63. 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. PubMed PMID: 23527071. Pubmed Central PMCID: 3602549.
64. Usui Y. [Expression and function of ICOS on CD4 T cells and application to therapy in patients with ocular Behcet's disease with uveitis]. *Nippon Ganka Gakkai zasshi*. 2012;116(11):1037-45. PubMed PMID: 23316652.
65. Cao J, Chen C, Zeng L, Li L, Li X, Li Z, et al. Elevated plasma IL-22 levels correlated with Th1 and Th22 cells in patients with immune thrombocytopenia. *Clinical immunology*. 2011;141(1):121-3. PubMed PMID: 21652269.
66. Cao J, Li L, Chen C, Liu C, Meng FJ, Zeng LY, et al. [Expression of interleukin-22 and relative CD4(+) T cell subsets in patients with immune thrombocytopenia]. *Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology*. 2012 Dec;20(6):1432-5. PubMed PMID: 23257448.
67. Wu CL, Wang Q, Zheng L, Gu DY, He JA, Shao CP. [Correlation of Breg with CD4(+)T Cells of Peripheral Blood in Patients with

- CITP and Its Clinical Significance]. *Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology*. 2013 Nov;21(6):1517-21. PubMed PMID: 24370040.
68. Hu Y, Li H, Zhang L, Shan B, Xu X, Li H, et al. Elevated profiles of Th22 cells and correlations with Th17 cells in patients with immune thrombocytopenia. *Human immunology*. 2012;73(6):629-35. PubMed PMID: 22537755.
69. Cao J, Chen C, Li L, Ling-yu Z, Zhen-yu L, Zhi-ling Y, et al. Effects of high-dose dexamethasone on regulating interleukin-22 production and correcting Th1 and Th22 polarization in immune thrombocytopenia. *Journal of clinical immunology*. 2012;32(3):523-9. PubMed PMID: 22289995.
70. Kiriakidou M, Cotton D, Taichman D, Williams S. Systemic lupus erythematosus. *Annals of internal medicine*. 2013;159(7):ITC4-1. PubMed PMID: 24081299.
71. 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. *The Egyptian journal of immunology / Egyptian Association of Immunologists*. 2012;19(2):25-33. PubMed PMID: 23885404.
72. 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. *Experimental biology and medicine*. 2013;238(2):193-9. PubMed PMID: 23576801.
73. 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. *Annals of the rheumatic diseases*. 2009;68(4):604-6. PubMed PMID: 19286907.
74. 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. *Scandinavian journal of immunology*. 2014;79(2):131-6. PubMed PMID: 24313261.
75. 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. PubMed PMID: 24056519.