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Expression profiles of different cytokines in the pathogenesis of autoimmune diseases

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Abstract. Autoimmune diseases(AID) have always been immune system diseases that affect millions of patients around the world no matter your race or age. Although the exact origins of most autoimmune diseases are still unknown, A growing body of research suggests that cytokines in vivo are closely related to the pathogenesis of autoimmune diseases. There are many kinds of cytokines that have been shown to contribute to one or even more kinds of AIDs. There are also many researches that focus on the relationship between a single cytokine and the pathogenesis of a specific type of AIDS. However, there are few overall discussions and summaries of the relationship between individual cytokines and common autoimmune diseases. Here, this review chooses the three most common AIDs: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriasis, and talk about the relationship of their pathogenesis with main cytokines, including TNF-α, IL-17, IL-1 and IL-6. By summarizing the relationship between these cytokines and the pathogenesis of these three types of autoimmune diseases, this review has a reference value for the clinical treatment and scientific research of these diseases, as it shows that some cytokines can work upstream and downstream of the same pathway.

Keywords: Autoimmune diseases, cytokines, inflammation, Interleukin, TNF-α.

1. Introduction

Autoimmune diseases (AID) are a group of diseases in which the body's immune system responds to its antigens by forming autoantibodies or auto-sensitized lymphocytes. These auto-antibodies or auto-sensitized lymphocytes may attack tissues or organs by targeting these antigens when the immune system is abnormal, causing damage to the body's tissues[1]. The main mechanism behind this is an abnormality of the immune response and immunoregulation. Although autoimmune diseases appear to be less common compared to other diseases, they still affect a significant portion of the population worldwide. The prevalence of autoimmune diseases has increased from 7.7% in 2000-2002 to 11.0% in 2017-2019[2]. Most autoimmune diseases are incurable and require life-long treatment. AIDS greatly impacts the daily working and quality of life of patients, threatens their lives, consumes a substantial amount of health resources, and has become an important public health issue affecting human health. There are nearly 100 types of autoimmune system diseases, including SLE, RA, psoriasis, and so on. In the last decade, significant progress has been made in diagnosis, disease classification, and treatment. When scientists search for the mechanisms of pathogenesis of autoimmune diseases, cytokines, as a significant component of the human immune system, have come into focus[3].

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Cytokines are small molecule peptides or glycoproteins secreted by various cells that have a crucial function within the development, differentiation, and functional modulation of immunocytes. The self-regulatory network of the body's immune system relies on the equilibrium of proinfliterative and anti-infliterative cytokines, and when the balance is disturbed, autoimmune phenomena and the generation of AID are induced. The cytokines that have been proven to have a connection with AIDS include TNF-α, IL-17, IL-10, etc[4]. Normally, the expansion and production of cytokines are tightly regulated by the human body, while in AID, cytokines are abnormally expressed, Therefore, the detection of cytokines has already become a crucial part of the diagnosis and treatment of AID. Many researchers have paid attention to the relationship between the key immune cytokines and AIDS, resulting in many studies that reveal the association between autoimmune diseases and cytokines being written and published[5].

However, the majority of common articles or papers all focus on one or two single cytokines and their relationship with a particular group of autoimmune diseases. Therefore, this review will not only discuss three significant and common autoimmune diseases in humans (systemic lupus erythematosus, rheumatoid arthritis, and psoriasis) but also the main cytokines related to their pathogenesis. After that, a conclusion about these diseases and their connection with several cytokines will be drawn, with some discussions about which cytokines are specific to one disease and which are shared across diseases. Additionally, the challenges and future perspectives of utilizing cytokines as a method of diagnosis and treatment of AIDS will be briefly addressed.

2. The autoimmune disease

2.1. Rheumatoid arthritis (RA)

RA is an autoimmune disease with a complex etiology. Its pathogenesis involves several factors, which makes the diagnosis and treatment of this disease difficult initially. It is prevalent in all countries, among patients of different races, ages, and genders. It is a chronic inflammatory disease of the joints that may lead to lifelong disability if not effectively treated and managed. The pathogenesis of rheumatoid arthritis remains controversial. However, it is now generally recognized that the infiltration of synovial inflammatory cells, as well as synovial hyperplasia, can cause joint damage, which results in skeletal destruction. This has now become the typical characteristic of RA[6].

The latest studies have indicated that there exists a sturdy connection between RA and certain immune cytokines in the human body. These cytokines form a vast network among themselves, interacting with various cells to cause a variety of inflammatory responses that result in damage to cartilage and joints. The most important cytokines involved in the pathogenesis of rheumatoid arthritis are the TNF-α and IL-6[7]. However, other cytokines like IL-7, IL-23, and IL-2 are found in recent research as well. The predominant autoantibody that triggers these cytokines is the rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA), which is also a significant serological marker of RA. ACPA and RF can stimulate macrophages and result in the breaking out of cytokines like TNF-α and IL-6, ultimately leading to RA[8].

2.2. Systemic lupus erythematosus (SLE)

SLE is another very usual chronic AID that appears to favor women. Although the reason why there are more female patients is not clear, it suggests part of the pathogenesis of this type of disease may be related to sex chromosome inheritance. However, the pathology of SLE is far from simple and is considered to be the outcome of a mix of environmental, genetic, and immune system factors. Symptoms of SLE are highly varied and often include fever, sensitivity to light, skin rashes, enlarged lymph nodes, muscle and joint pain, headaches, and fatigue. The disease can damage organs throughout the body and therefore may cause a variety of complications, including kidney damage and neuropsychiatric symptoms. Symptoms may vary from patient to patient and may be mild or severe as the disease goes into remission or relapses. It is a very complex disease and there is almost no complete cure[9].

However, there are also studies showing that several pro-inflammatory cytokines are associated with SLE, such as IL-6 and TNF-α. Additionally, other cytokines like IL-17 and Th1 cell family which

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includes Th1 cells, and related cytokines like IL-18, TGF-β, and IL-12. Toll-like receptors (TLRs) are a type of pattern recognition receptors (PRRs) that serve a vital function in the natural immune system. Studies have shown that patients with SLE have overexpressed TLRs in dendritic cells and B cells, which causes a massive production of these inflammatory cytokines. Thus the TLRs have become an important part of the pathogenesis of SLE[10].

2.3. Psoriasis

Psoriasis is one of the autoimmune-induced skin disorders, labeled as erythema, induration, and scaling. These symptoms are due to changes in the skin's stratum corneum caused by inflammation. Psoriasis occurs all over the world. The cause of psoriasis is still unclear, however, it is recognized to have connections with a combination of factors like genetics and environmental influences. The disease has been associated with factors such as meridians, food habits, climatic seasons, and family history. There are several types of psoriasis, the most common being the plague type, in addition to the arthropathic, pustular, and erythrodermic types. The causes of psoriasis are varied and include smoking, alcohol abuse, drug reactions, skin damage, bacterial infections, genetics, and immune factors. Psoriasis not only affects the skin, but also the heart, nervous system, intestines, and kidneys. This can lead to a number of other diseases such as cardiovascular disease, depression, and inflammatory bowel disease[11].

Psoriasis has already been found to have a significant connection with cytokines. The pathogenesis of psoriasis is related to various types of cytokines like the IL-17 as well as the IL-1 family [12]. Keratinocytes(KCs) and the dendritic Cells,(DCs) are both involved in the process of psoriasis. Inflammatory mediators such as antimicrobial peptides produced by KCs damage activate DCs. Abnormally activated DCs and the cytokines they produced such as IL-23 and IL-12 activate corresponding T cells as well as produce inflammatory factors. For example, IL-17A and IFN-γ. These factors lead to an increased inflammatory response in psoriasis and stimulate the aberrant proliferation of KCs, exacerbating the development of psoriasis.

3. The connection between AID and cytokines

3.1. TNF-α

In 1975, E.A. Carswell et al. found that after the administration of bacterial lipopolysaccharide into BCG-vaccinated mice, a compound capable of causing bloody necrosis in many tumors present in the blood, which they called it tumor necrosis factor(TNF). The tumor necrosis factor superfamily (TNFSF) includes 19 members with 29 corresponding receptors. Among them, TNF-α, the first discovered TNF, is the most important member, accounting for around 80% of the total TNF activity.

TNF-α is a well-known inflammatory cytokine primarily produced by activated T cells and NK cells. It was also the pioneer cytokine which is used for tumor immunotherapy. TNF-α is strongly associated with several autoimmune diseases, including those mentioned above.

For rheumatoid arthritis (RA), research suggests that TNF-α has become a major part of its pathogenesis. Various cells are involved in the inflammatory response, including helper T cells, macrophages, B cells, and DCs. The TNF-α is produced from type-1 helper T cells(Th1) and macrophages. TNF-α can activate the synovial fibroblasts to stimulate epidermal hyperplasia and enroll inflammatory cells. Synovial fibroblasts overexpress histone proteases and matrix metalloproteinases (MMPs), leading to the decomposition of collagen and proteoglycans. Consequently, cartilage and bone are damaged, ultimately resulting in joint erosion.[13].

For psoriasis, TNF-α is also involved in the inflammatory pathways of its pathogenesis. Stressed keratinocytes overproduce TNF-α, triggering the stimulation of dendritic cells(DCs). The DCs then secrete IL-12 to drive the immature T cells into Th1 cells, and IL-23 converts infantile T cells to Th17 cells. Th1 cells and Th17 cells each overexpress TNF-α and IL-17 respectively. Excess TNF-α and IL-17 lead to hyperproliferation of keratinocytes and epidermal alterations, ultimately resulting in psoriasis[14].

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In the pathogenesis of SLE, immune cytokines also play an indispensable role. TNF-α is also included and has a unique effect in both immunosuppressive and proinflammatory pathways. On the one hand, it promotes the growth and development of B cells, macrophages, and dendritic cells, and on the other hand, it acts as a regulator of the inflammatory response and can lead to apoptosis. So its role in SLE is complex, it mobilizes the immune system to fight infections, but it can also have serious consequences because of the apoptosis it induces[15].

3.2. IL-6

Interleukins are a group of cytokines that are manufactured by and act on a variety of cells. They were originally produced by leukocytes and act among leukocytes, hence its name, which is still used today. Now interleukins refer to a class of cytokines whose molecular structure and biological function have been partly clarified and have an important regulatory effect. These cytokines are named in a unified way and belong to the same class of cytokines.

Interleukin 6 is an essential element of the cytokine web and is the core of the acute inflammatory response. Discovered by Weissenbach in 1980, IL-6 is a polyfunctional cytokine that has a major function in human metabolism, autoimmune cell differentiation, and disease therapy. IL-6 is crucial for both the innate and adaptive immune systems[16].

When it comes to rheumatoid arthritis (RA), IL-6 is always an indispensable member in its development. IL-6 is made by many types of cells, including monocytes, T lymphocytes, and fibroblasts, its production is greatly increased at sites of inflammation. A large amount of IL-6 is produced and binds to its own receptor, IL-6R, and glycoprotein 130 (gp130). After activation, the binding body affects tyrosine-protein kinase 1 and 2, which ultimately results in the production of a large number of cytokines, such as TNF-α, and IL-17, triggering arthritis[17]. In addition, IL-6 can also cause a variety of immunoglobulins to form rheumatoid factors, leading to severe antibody deposition in the synovium of RA patients, impairing the joint function of RA patients, and leading to exacerbation of their condition.

T cells, monocytes, and endothelial cells are implicated in SLE pathogenesis too, and they can all produce IL-6. Although the concrete mechanisms by which IL-6 causes SLE are still unclear, increased blood levels of IL-6 were observed in SLE patients. Additionally, experiments on mice have shown that monoclonal antibodies against IL-6R are effective in SLE treatment. Despite the lack of evidence that IL-6 directly affects the pathogenesis of SLE, the effects of IL-6 on the cardiovascular and complement systems of patients are relevant to the cardiovascular disease caused by SLE[16].

3.3. IL-17

IL-17 is an inaugurator of early T cell-inspired inflammatory responses and can ameliorate the institutional response by facilitating the liberation of pro-inflammatory cytokines. IL-17 plays a significant role in fighting against bacterial and fungal infections as well. IL-17 is mainly secreted by specific CD4+ T cells, which are called Th17 cells. IL-23 and TNF-β are involved in the maturation of naive T cells into Th17 cells. The IL-17 family consists of six members. The first cytokine identified included IL-17A, which is called IL-17. It is deeply studied as well. IL-17A is associated with the pathogenesis of several autoimmune diseases, such as psoriasis, RA, and SLE.

IL-17 family-specific membrane receptors (IL-17R) take part in the IL-17 signaling pathway. After binding to IL-17R, IL-17 exerts its biological effects through the mitogen-activated protein(MAP) kinase pathway and the nuclear factor kappa-B (NF-κB) pathway. Through these pathways, IL-17 effectively mediates the mobilization of neutrophils, thereby contributing to the inflammatory response in tissues[9].

In SLE, IL-17 works with IL-23 and IL-21 to form an elaborate net that triggers an inflammatory response, inducing tissue damage as well as initiating the secretion of additional pro-inflammatory cytokines. IL-17 also regulates B cell survival, proliferation, and differentiation into plasma cells, resulting in autoantibody synthesis. As a result, immune complexes accumulate in the target organ, complement is triggered, and there is an enhanced exposure to the common organ damage in patients

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with SLE. IL-17 exacerbates SLE activity by enhancing the migration of immune cells and sustaining exaggerated inflammatory response[4].

In RA, the IL-23/IL-17 axis is also an indispensable part of pathogenesis. IL-23 leads to the mature of Th17 cells. Th17 cells exist in synovial joints and produce IL-17, which promotes osteoclastogenesis in conjunction with TNF and IL-6. IL-17 participates in two kinds of RA, advanced and established. It stimulates the turning on of fibroblast-like synoviocytes (FLS), osteoclast formation, enrollment process induction, and promotion of macrophages, and B-cells[13].

IL-17 has always been a crucial member of the pathogenesis of psoriasis. The mechanism of psoriasis involves a dynamic interaction between T cells (CD8+, Th1, autoreactive T cells, Th17 and Th22) and dermal dendritic cells(DDCs). Within the dermis, IL-23, produced by DDCs, can trigger the revitalization of Th17 lymphocytes and the subsequent release of pro-inflammatory cytokines, such as IL-17A and IL-26. IL-17A and IL-22 interact with keratin-forming cells (KCs), resulting in epidermal hyperplasia, acanthosis nigricans, and hyperkeratosis[11].

3.4. IL-1

IL-1 is considered the quintessential pro-inflammatory cytokine and has been studied since the 1940s for its thermogenesis and pro-inflammatory properties, hence IL-1 was the first cytokine to be measured in the skin. It is produced primarily by activated monocyte macrophages. The IL-1 family has three significant members, including IL-1α, IL-1β, and IL-18. IL-1 also plays a modulatory role in the optimization of cellular immunity. These cytokines use the same receptor compositions, IL-1R1 and IL-1R3, for signaling. IL-1 is induced by a variety of stimulatory factors including antigens, endotoxins, bacteria, and viruses, and becomes a crucial part of the pathogenic process of acute and chronic inflammation, and is closely related to the pathological process of some autoimmune diseases such as psoriasis and rheumatoid arthritis.

IL-1β has already been proven to be a key member in the progression of RA. Natural killer (NK) cells and neutrophils can secrete IL-1β. IL-1β is known to mobilize monocytes/macrophages, which enhances inflammatory response. It also triggers the growth of fibroblasts, leading to the proliferation of the synovium. Furthermore, IL-1β stimulates chondrocytes, resulting in chondrogenic damage, causing bone resorption[17].

IL-1 was detected in the skin of the psoriasis patients as well. The two IL-1 forms, IL-1α and IL-1β, are both found in healthy epidermis. Once secreted, these two IL-1 subtypes have comparable functions in that they can both interact with keratinocytes as well as on localized fibroblasts, vascular endothelium, and lymphocytes. IL-1 rapidly and profoundly affects keratinocytes, causing its transition from the common form to the psoriatic form. Furthermore, IL-1 is a critical cytokine in the progression of the Th17 response in psoriatic skin. IL-1 works together with IL-23 to help T cells develop into Th17 and secrete IL-17[5].

IL-1 family also shows a strong connection with SLE. Former studies have suggested that IL-1β takes part in murine lupus-like models. IL-1β levels are positively related to disease severity. Also, another member of the IL-1 family, IL-18, participates in the progress of SLE. IL-18 plays a central function in the Th1 reaction by triggering the creation of IFN-γ in CD8+ T cells and NK cells. With the help of IL-18, Th1 cells produce IL-1β and TNF-α, which contribute to the inflammation responses in SLE. In addition, the serum IL-18 levels have been considered to reflect the extent of renal injury in SLE[17].

4. Conclusion

Autoimmune diseases (AID) are characterized by an abnormal immune response of lymphocytes and/or antibodies due to an imbalance in normal immune self-stabilization, where the body's immune system produces an immune response against its own tissue components. The origin and progression of autoimmune diseases all have a strong connection with an imbalance of immune cells and cytokines in the body.

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Cytokines are key immune mediators that activate immune response and differentiate the immune cells, enable host defense, and restore homeostasis. On the other hand, excessive or sustained cytokine production leads to dysregulated immune activation and affects the initiation and amplification phases of immune pathologies.

There are some cytokines that take part in all the three autoimmune diseases talked about above, including TNF-α and IL-17. Some cytokines only work in a single or two autoimmune diseases and their function in other autoimmune diseases is still not quite clear. It is easy to confirm that the different kinds of cytokines can stimulate or interact with each other, forming a complex network in the human body, which not only deals with the immune response but also has a great connection with the pathogenesis of autoimmune diseases. Many studies have already been made to reveal the relationships between cytokines and different AIDs, and more and more medicines that target specific cytokines to cure AIDs have been put into clinical trials. It is foreseeable that in the near future, the role of cytokines in autoimmune diseases will be more and more emphasized and more and more new research has been new theories. Cytokines will also become the key to revealing the pathogenesis of some autoimmune diseases and serve as hard indicators of the degree of disease in patients. Here is a table that briefly makes a summary of this review (Table 1).

Table 1. The summary of the three AIDs and their related cytokines

Diseases	Related cytokines(Mainly)	targeted drugs	Related signaling pathway
RA	TNF-α, IL-6	Infliximab(Anti-TNF-α); Tocilizumab,(Anti-IL-6)	TNF-α activates synovial fibroblasts, stimulates epidermal proliferation, and attracts inflammatory cells, promoting excessive expression of MMPs, leading to cartilage degradation.
Psoriasis	IL-17,IL-1	Secukinumab(Anti-IL-17); Anakinra,(Anti-IL-1)	IL-1 can interact with keratinocytes as well as on localized fibroblasts, vascular endothelium, and lymphocytes. IL-1 has a quick and deep effect on keratinocytes, causing its transition from the common form to the psoriatic form.
SLE	TNF-α,IL-17	Infliximab(Anti-TNF-α); Secukinumab(Anti-IL-17)	IL-17 cooperates with different cytokines to form a complicated net that triggers inflammation and creates organic damage.

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