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Effects of Interleukin Families Polymorphisms on Systemic Lupus Erythematosus: Focus on Interleukin-1

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Abstract

Systemic Lupus Erythematosus (SLE) is a chronic human autoimmune disease, which is characterized by increased activity of B cells and production of antibodies against tissue antigens. It engages many tissues and organs, including joints, kidneys, heart, and the nervous system. Although the exact pathogenesis of SLE remains to be elucidated, it is suggested that genetic background plays a paramount role in SLE etiology. Increasing evidence is indicating an important role for interleukins in progression of SLE. Interleukins are a group of cytokines secreted by T helper cells, monocytes, macrophages, and B cells, which are involved in growth and differentiation of T and B cells. The expression level of interleukins is influenced greatly by genetic composition. Therefore, some polymorphisms can control the expression of interleukins. Consequently, genetic studies can shed light on our understanding of SLE nature. Therefore, in the present study, the researchers reviewed the roles of eight key interleukin polymorphisms and their effects on SLE pathogenic.

Keywords: Interleukin-1, Cytokines, Systemic Lupus Erythematosus, Polymorphism

1. Background

Systemic lupus erythematosus (SLE) is a chronic human autoimmune disease, which engages various human organs. It is characterized by increased activity of B cells and over production of antibodies against endogenous antigens. Accumulation of antibodies in tissues and organs plays a key role in clinical signs of SLE (1, 2). Lupus mostly effects the kidneys, heart, and the nervous system. The joints are affected more in some specific SLE types and the skin is affected in all types of lupus (3, 4).

The prevalence of lupus in different populations ranges from 20 to 150 cases per 100,000 individuals around the world (2). Moreover, in females of the reproductive age, SLE is about nine times more frequent than males, and its incidence is variable in different races, ethnicities, geographic regions, and social and economic status. This disease is not common in children younger than 15 years old, and consists of about 20% of the patients (5).

The exact pathogenesis of SLE remains to be elucidated, yet genetic and environmental factors play an important role in SLE pathogenesis (6-8). Understanding complicated genetic background of lupus and determining the number of genes involved, is a heavy burden (9). Seemingly, lupus stemmed from loss of tolerance to insider's antigens and then production of antibodies against the cell's nucleus (10, 11). Generally, lupus is categorized to four groups, including discoid lupus, drug-induced lupus, neonatal lupus, and systemic lupus erythematosus (12).

Interleukins (IL) are a group of cytokines, secreted mostly by T helper cells, monocytes, macrophages, dendritic cells, natural killer cells, and B cell. The interleukins are mainly involved in growth and differentiation of T and B cells and activate natural killer cells. It has been shown by

several studies that the role of inflammatory interleukin gene's polymorphisms in creation of SLE is of paramount importance. Interleukins involved in SLE include interleukin 1 (13), interleukin 1 beta (14), interleukin 4 (14), interleukin 6 (15), interleukin 7 (16), interleukin 10 (15), interleukin 21 (17), interleukin 19 (18), interleukin 27 (19), interleukin 31 (20), and interleukin 32 (21).

Knowledge on interleukins can cast light on our knowledge of SLE and leads to early diagnosis and development of novel treatment methods. In the present article, the role of inflammatory interleukin genes, especially the Interleukin 1 gene family, in creating the SLE was reviewed.

2. Interleukins Involved in Systemic Lupus Erythematous

Cytokines are secreted by cells involved in the immune system, including T cells and other immune response cells. According to T cell types, some cytokines play inhibitory roles while, some others play excitatory roles. Maintaining Th1/Th2 balance is a key factor for immune homeostasis, the distortion of which is supposed to be the cause of SLE. However, there is no comprehensive information on the relationship between Th1 and Th2 levels; however, it is clear that increasing levels of Th2 is a crucial step in progression of SLE. On the other hand, reducing levels of Th1 are involved in progression of SLE. There are many important Th1 and Th2 cytokines, involved in the pathogenesis of SLE, such as IL-12, IL-4, IL-10, and IL-6 (4, 22, 23).

Genetic composition is a determinative factor in controlling production of interleukins and, it has been elucidated that presence of some polymorphisms can increase or decrease the expression of interleukin genes, and in turn, increase the susceptibility to certain diseases (24). Studies concerning the association between interleukins and SLE are reviewed below.

2.1. Interleukin 23 (IL-23)

Interleukin-23 is believed to be an important factor in pathogenesis of autoimmune diseases. It was recently reported that IL-23 abnormalities contributed to the development of SLE. Interleukin-23 is able to stimulate TCD4 production of pro-inflammatory cytokines, such as IL-17 and IFNγ. This cytokine plays an important role in progression of SLE. Also, clinical and pathological signs of SLE nephritis were decreased in defect of IL-23 receptors. Therefore, it seems that IL-23 is an essential factor in damaging the kidneys in patients with SLE (25, 26).

2.2. Interleukin 21 (IL-21)

Interleukin-21 is produced by follicular T cells. This cytokine induces differentiation and development of T helper cell, and stimulates the production of antibodies by B cells (27). It has been reported by previous studies that plasma level of IL-21 is increased in patients with SLE.

Variations in the IL-21 gene may lead to change in the IL-21 protein, which subsequently alters the susceptibility of individuals to SLE. Several polymorphisms in the IL-21 gene have been identified in association with SLE (28-30). Recently, some studies showed that IL-21 increases inflammatory diseases and autoimmune chronic diseases in humans. Also, animal studies reported that IL-21 plays an important role in the pathogenesis of SLE, and its serum level in SLE patients was higher compared with the control group. In addition, some other studies indicated the association between IL-21 and its receptor polymorphism with SLE susceptibility (31).

2.3. Interleukin 18 (IL-18)

Interleukin-18 is a member of the IL-1 family. Inactive IL-18 is cut by caspase-1 to be converted to the biological active form. Its biological function includes influencing of dendritic cells, T lymphocytes and natural killer cells, and inducing IFN-A to increase differentiation of Th1 (32). Elevated concentration of IL-18 in patients with SLE has been introduced by previous studies. Moreover, it has been reported that IL-18 level is associated with urine microalbumin level and kidney malfunction in patients with SLE (33-35). In addition, IL-18 gene expression is increased in the glomeruli of patients with SLE nephritis (35). Also, overexpression of IL-18 is a cause of skin lesions in patients with SLE (36).

2.4. Interleukin 17 (IL-17)

Interleukin-17, a pro-inflammatory cytokine, is a key regulator of inflammation process. Six members of the IL-17 family, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F, have been recently reported to be involved in SLE, which, are primarily released by activated T lymphocytes (37, 38). Furthermore, IL-17 induces B cell proliferation and subsequently antibodies production. Also, elevated serum levels of IL-17 has been reported to be associated with development of SLE (25, 26, 39). In SLE patients, IL-17, released by T lymphocytes, induced T cells and mRNA molecules adhesion to endothelial cells (40, 41).

2.5. Interleukin 10 (IL-10)

Interleukin-10 is suggested to be directly involved in T cells suppression. Also, this interleukin plays an important role in B cells activation. Interleukin-10 is mainly released

by activated macrophages and also at lower amounts, by other cell types, such as T cells and keratinocytes (42). The serum levels of IL-10 are increased in SLE patients and this is related with disease severity. This interleukin stimulates the proliferation and differentiation of B cells. Also, IL-10 effects the expression of Bcl-2 and decreases the apoptosis rate in B cells. Therefore, it can enhance antibody production.

Recently, studies have shown that IL-10 injection to mice with SLE lead to escalated kidney damage in SLE (25, 26, 43). Also, it was reported by many studies that various polymorphisms in the promoter region of the IL-10 gene is associated with SLE (44-46). However, findings are still controversial since another study reported no significant association between IL-10 polymorphisms and susceptibility to SLE (47).

2.6. Interleukin-6 (IL-6)

Interleukin-6 (IL-6) production is promoted by TNF and IL-1 and it has pleiotropic effect on many tissues in humans. Interleukin-6 is mainly secreted by macrophage cells and in lower amounts by mesangial cells, endothelial, and lymphocytes (25). Interleukin-6 increases the activation and secretion of macrophage, B lymphocyte, and immunoglobulin. Also, IL-6 can promote differentiation of Th17 cells, which plays an important role in many autoimmune diseases. Elevated levels of IL-6 in serum and urine samples of SLE patients has been observed (26). Moreover, IL-6 and renal malfunction association was also considered recently (48).

2.7. Interleukin 4 (IL-4)

Interleukin-4 is an anti-inflammatory cytokine, which is produced by Th2 $CD4^+$ cells on the surface of Basophils and Mast cells (49). Interleukin-4 protein, as a key cytokine, promotes activation and differentiation of B cells and is also involved in development of T cells (50). This cytokine also has a flip side cytotoxic effect and triggers inhibition of nitric oxide synthase, release of dismutase anions by macrophages, and some other anti-inflammatory effects. The role of IL-4 is well-known in autoimmune diseases. It was implied by various studies, including recent findings by the current authors, that the effect of IL-4 on SLE development is closely contributed with its gene polymorphism (14, 51, 52).

3. Interleukin 1 Family

Interleukin-1 (IL-1) gene cluster is, a 430-kb region, including IL-1α (IL-1A), IL-1β (IL-1B) and Receptor Antagonist of Interleukin-1 (IL-1RN) genes. Different studies have found significant differences in expression level of IL-1 family among patients with SLE and healthy subjects (13, 24). Interleukin-1A and IL-1B proteins are pro-inflammatory cytokines and play important roles in extensive biological processes. Furthermore, IL-1A and IL-1B bound to IL-1 receptor trigger signal transduction, followed by biological effects. On the contrary, IL-1Ra protein is a competitive inhibitor, which binds to IL-1 receptors and inhibit intracellular signaling (53). It is believed that expression imbalance of these three proteins and their receptors may play an important role in creation of autoimmune diseases.

4. Interleukin 1 and SLE

Interleukin-1 protein family includes IL-1 alpha (IL-1α), IL-1 beta (IL-1β), and IL receptor antagonist (IL-RA). Interleukin-1 is located on chromosome 2 (2q13-21), in the 430-kb region, and IL-1α and IL-1β genes are very close together (54, 55). Interleukin-1α and IL-1β are pro-inflammatory cytokines, which are involved in many biological activities. Studies suggested that imbalance between IL-1α, IL-1β, and IL-RA proteins can cause autoimmune response (53). Many studies reported a significant relationship between abnormal expression of IL-1 and progression of SLE, which was firstly revealed in 1983 (56-59). However, more investigations are needed to clarify the relationship between IL-1 member's polymorphisms and SLE. Chua et al. (2009) showed that IL-1β -511C/T polymorphism increases SLE susceptibility in the Malaysian population (60). Furthermore, Parks et al. (2004) reported that T allele increases susceptibility of SLE in the African American population (59). Also Huang et al. (2002), reported no relationship between IL-1β -511C/T polymorphism and SLE in a Taiwanese population (61). In a similar study Chua et al. (2009), a significant association was reported between IL-1β + 3954E1/E2 (heterozygote) polymorphism in exon 5 and SLE in the Malaysian population, and E1 (wild allele) allele increased the SLE risk (60). Also, this result has been reported in a Columbian population, yet not in the Chinese population (62, 63).

The activity and production of IL-1α and IL-1β are controlled by IL-receptor antagonist (IL-1RA or IL-1RN). Deregulation in expression of IL-1 by IL-1RA, and abnormal activity leads to high inflammatory response and causes damage to tissues, which is one of the SLE symptoms. Many studies have been performed to evaluate the association between IL-1RN gene polymorphisms and SLE. Interleukin-1RA variable numbers of tandem repeat -86 bp (VNTR 86-bp) polymorphism in intron 2 is reported to be relevant with SLE risk (64, 65). A previous study by the current authors in association between VNTR 86-bp polymorphism and SLE showed that IL-1RN*2 allele had no association with SLE

(13). On the other hand, Blakemore et al. found an association between the IL-1RN*2 allele and SLE susceptibility (65). Also, Lian et al. showed that IL-1RN*2 allele is associated with SLE in the Malaysian population (66).

5. Conclusions

In the present study, the researchers focused on some interleukins, which play important roles in SLE pathogenesis. Systemic Lupus Erythematosus is an autoimmune disorder with many heterogeneous symptoms. The main mechanism of this disorder remains to be elucidated. Besides, many studies suggested that SLE is a multi-factorial disease, which involves genetic, environmental, and immunological agents. These factors increase body sensitivity toward antigens; therefore, immunologic responses become out of control in some tissues, which cause damage. Many studies performed on SLE patients and SLE animal models have shown that over expression of some members of the interleukin family have significance contribution on SLE progression. Over expression of some inflammatory interleukins lead to B cell auto-reaction, which in turn, increases the production of autoantibodies.

Footnote

Conflict of Interests: The authors declare no conflicts of interest.

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