

Current Pathogenesis and Treatment of Autoimmune Diseases

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Abstract. Nowadays, autoimmune diseases(AD) still torment many people and they always suffer from severe symptoms and complications. However, the pathogenesis of AD is still unclear and needs more research. Also, there are shortages of treatments which can totally cure AD. This research mainly focuses on current findings of possible pathogenesis and treatments for AD by discussing and analyzing two of most famous AD: rheumatoid arthritis and systemic lupus erythematosus (SLE). This essay discusses pathogenesis of RA and SLE from three aspects: genes, immune systems and environmental factors, and then concludes current medications and therapies as well as their drawbacks. This study finds that susceptible genes, abnormal immune responses and environmental stimulation can synergistically lead to autoimmune diseases, and existing treatments are mainly composed of symptomatic treatments and modifying treatments. But each medication has its inevitable side effects. Furthermore, more research should focus on systematic treatments with fewer drawbacks in order to truly cure AD.

Keywords: Autoimmune diseases; immunology; pathogenesis; treatment.

1. Introduction

Autoimmune disease (AD) refers to a collection of varied illnesses with a wide range of clinical presentations in which aberrant immune responses target healthy cells. Up to now, there are at least 80 related diseases [1]. In America, approximately 7% of population have AD. And morbidity of women is higher than men's [1]. The relatively most common AD are rheumatoid arthritis(RA) as well as Systemic Lupus Erythematosus (SLE). RA patients may develop symptoms of pain and tumidness in joints, and they even trigger heart-lung inflammation, which threaten people's health to a large extent. Nearly 0.5%~1% of population in developed country have RA. SLE may cause facial erythema, arthritis and other symptoms. Almost 0.02%~0.07% of population contract this disease [2]. The longevity of patients with SLE significantly shorter than common people. However, current treatments of AD still have drawbacks and side effects. What's worse, most treatments can only alleviate symptoms but not totally cure AD. So far, the pathogenesis of AD still needs further exploration and research in order to find more accurate treatments. Due to existing a variety of statements and methods, It's very necessary to conclude a clear system based on research, there by offering practical solutions.

This research summarizes and analyses the possible pathogenesis of both RA and SLE based on different causes and factors, then compares the pathogenesis of RA with LE and summarizes the similarities and differences. Also, this study pairs up different treatments with relative pathogenesis of RA and LE, finding new promising treatments.

2. Epidemiology

2.1. Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) mainly targets joints, which always causes joint fever, makes joints swollen and painful. One of critical symptoms of RA is morning stiffness, which commonly lasts for an hour or more. Targeted joints at first appears to be asymmetrical. As disease develops, Symptoms become symmetrical. Specifically, this disease usually begins with hands and feet but also has the risk of threatening other part of body. The symptoms of RA regularly last weeks or months, accompanied by anemia, lung-heart diseases. What's worse, it may even trigger interstitial lung

diseases (ILD) like pulmonary fibrosis. Most of RA patients died because of RA-ILD. Nearly 10%~20% of patients may develop symptoms in lungs earlier than in joints [3]. The morbidity of RA of female is 250% of male's [1].

2.2. Systemic Lupus Erythematosus (SLE)

The relatively most common type of lupus erythematosus is Systemic Lupus Erythematosus (SLE). Some common symptoms are erythema, arthritis, fever, and chest pain. The amounts of cases of marriageable women are nine times as much as cases of man [4]. SLE is a significant burden for pregnant women because they are at high risk of giving birth, and even they may experience foetal loss and preterm births. The worldwide occurrence of SLE ranges from 1.5 to 11 per 100,000 person. This significant variation of incidence of SLE partially results from distinctions in population structure like sex distribution, ethnicity and environmental factors [2]. Nonetheless, this disease still severely influence patients longevity because patients usually live shorter than normal people.

3. Pathogenesis

3.1. Rheumatoid arthritis (RA)

There are several factors can trigger RA. Firstly, RA may be caused by genetic factors. According to research, though, between identical twins, the concordance of RA is only approximately 15%, the whole heritability is calculated to be about 66% [5]. Specifically, in the HLA class II part on chromosome 6, there is genetic variants posing strong risk of many diseases of immune system, like RA. Also, HLA-DR1 and HLA-DR4 susceptibility genes prevent the immune system from recognizing citrullinated proteins as self-components. Those normal body parts are seen as antigens, which are delivered by antigen-presenting cells (APC). APC tend to initiate immune responses. Consequently, genetic factors contribute to abnormal immune responses. This process triggers the lymph node to produce CD4⁺ helper T cells, thereby exchanging signals with them. The whole process is named as co-stimulation [6]. Then, those T cells begin to interact with B cells. Plasma cells are produced by B cells due to signals from T cells, and then emit autoantibodies. Autoantibodies are unable to distinguish self from non-self-structures. Therefore, normal tissues and organs are attacked. As a result, a large amounts of antibodies like rheumatoid factors (RF) and autoantibodies binding to citrullinated antigens (ACPA), T cells and other immune substances like antibodies accumulate in the synovial fluid. Then, inflammation and tumidness occur in joints. To be specific, RF is detected at a level of 85% specificity among RA patients [6]. Cyclooxygenase (COX) and prostaglandin (PG) are quite active and very commonly exist in inflammatory parts, triggering severe pain. Genetic factors are able to contribute to some complications of RA, especially ILD. The MUC5B promoter variation, that is associated with airway cleaning and defense against multiple bacteria, has been proven to be the strongest genetic factor for RA-ILD, with more than 50% of RA patients developing related diseases [7].

Apart from that, the environment also contributes to RA to some extent. Smoking, dust exposure and microorganisms are able to influence the internal environment and homeostasis. A study shows that RA patients with more than 25 years smoking history had 310% more chances to be positive for RF, and the rate of experiencing joint erosions is 240% more than patients who don't smoke. At the micro level, smoking and inhaled pro-inflammatory agents like dusts, may promote protein citrullination in lungs. Those self-proteins are modified by smoking, thus becoming autoimmune targets [7]. Therefore, RA-ILD is triggered and threatened patients lives to a large degree. Nitrates and sulfur dioxide may be important contributors to RA, and these pollutants, PM inhalation can stimulate NF-KB, and then stimulate T helper cells to initiate cytokines, which make dendritic cells mature. Consequently, Auto-antigens are offered to self reactive T lymphocytes, thus moving to self tissues, causing joint's inflammation [6]. A lower level of ultraviolet B (UVB) radiation may lead to a simultaneous decrease in the amount of 1,25-dihydroxyvitamin D₃ production inside the skin.

However, this substance controls the immune system by stimulating the vitamin D receptor (VDR). RA may therefore be brought on by the comparatively weak immunomodulatory actions.

3.2. Systemic Lupus Erythematosus (SLE)

It is multiple factors that work together and result in SLE. At the genetic level, several genes are responsible for the disease susceptibility. According to existing research, approximately at least 4 susceptible genes are important components to develop SLE. Specifically, There are many studies related to the genes called major histocompatibility complex, which may be greatly associated with SLE. In MHC gene systems, the HLA class III genes, especially the encoding complements C2, C4, pose a higher risk to have SLE in particular ethnic groups. What's more, homozygous C4A null alleles bring higher risk of having the disease, without considering the ethnic origin [8]. Apart from that, many genes other than MHC genes also have potential to cause SLE. Genes coding for tumor necrosis factor α , the T cell receptor, heat shock protein 70 and so on, are associated with this disease.

The Immunopathology is also a necessary aspect. Patients with SLE always suffer from inflammation and blood vessel abnormalities, including immune complex deposition. To be specific, the autoantibody production can disturb the central immune system. Antinuclear antibodies are quite common among SLE patients. Only almost 5% patients don't have them. ds-DNA and anti-Sm antibodies are special to them [8]. Additionally, abnormal immune responses are also one of main causes of SLE, including B cells, T cells and some other related cells involving in specific immunity. Superfluous and uncontrolled T cells are able to trigger B cells to differentiate and produce antibodies [8]. The production of autoantibodies by B cells can react with self-antigens, which can occur years before the clinical onset of SLE. The abnormal production of autoantibodies will trigger an inflammatory cascade. Therefore, organs such as skins, veins and joints are damaged in SLE patients. B cells also secrete cytokines which make inflammation more serious [9]. As a result, these antibodies target normal blood vessels, leading to vasculitis. And the accumulation of immune complex in blood vessels, joints, even kidneys. Patients with active SLE have an increasing amount of activated B cells, and they are more susceptible to stimulation from cytokines like IL-6. Also, SLE patients have significantly abnormalities in T cell function, with the reduction in peripheral blood T cells. The interaction of those various abnormalities between immune systems and genes may be a possible pathogenesis of SLE.

4. Treatment for AD

4.1. Rheumatoid arthritis (RA)

Nowadays, one of the most common symptomatic treatments (mainly alleviate pain) of RA is nonsteroidal anti-inflammatory drugs—NSAIDs. It contains acetylsalicylate, naproxen, ibuprofen, and etodolac, which are partially effective to alleviate pain and reduce the level of inflammation. NSAIDs have various anti-inflammatory abilities, for they can inhibit prostanoid biosynthesis. NSAIDs is able to inhibit the enzyme activity of the COX, thereby inhibiting the production of PG in the location of inflammation and alleviating pain. However, the side effects of reducing PG contain bleeding and gastrointestinal problems. Other anti-inflammatory drug, such as corticosteroids, can bind to receptors of glucocorticoid in order to prevent inflammation. But the drawbacks of those drugs include nausea, diabetes, ulcers and so on. Another important symptomatic treatment is Glucocorticoid (GCs), including prednisone, hydrocortisone, prednisolone, dexamethasone. GCs are anti-inflammatory drugs with strong effectiveness that postpone radiologic progression in early disease stages of the disease by inhibiting gene expression related to RA. This treatment is more effective, and has more influence than NSAIDs because of its complicated mechanisms. Also, GCs play an important role in transition to DMARDs until they work. However, NSAIDs have a better safety profile. If patients use GCs for a relatively long time, the side effects of GCs may cause weight gain, muscle weakness and bone thinning [6]. Therefore, GCs can be given in the short-term treatment. To be specific, they may be taken orally, intravenously and intramuscularly.

A prevalent disease modifying treatment (manage the source of disease) is DMARDs such as methotrexate (MTX), hydroxychloroquine, chloroquine ought to be used once RA is diagnosed. There are more than one kind of DMARDs, such as conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs) and target synthetic DMARDs (tsDMARDs). DMARDs are drugs that treat rheumatoid inflammation by preventing more serious joint harm. In contrast to drugs which are unable to prevent disease progression like NSAIDs or pain medication, DMARDs have the ability to reduce RA symptoms, enhance physical function, and stop additional structural joint degeneration. Specifically, MTX is also a kind of antimetabolite, which can inhibit the activity of spinal cord, thereby mitigating inflammation caused by some leukocytes. MTX is recommended to be applied with a few doses of glucocorticoids to efficiently mitigate joint inflammation in a timely manner. With this initial treatment, 30%–50% of early RA patients can have either remission or low disease activity. Furthermore, MTX may have effects on many other enzymes such as methyltransferases, which play an important role in both B- and T cell function, being quite critical to targeting immunological factors of pathogenesis. csDMARDs are more commonly used than other methods without higher efficacy. But now, there is a trend towards a wider use of bDMARDs, which are genetically engineered proteins molecules. They have revolutionized the treatment of RA. There is a significant increase in the annual popularity of bDMARDs from 0.35% to 1.54% between 2004 and 2011 [6]. A large number of RA patients with a terrible response to csDMARDs gave feedbacks that bDMARDs can work effectively to a large extent. Nevertheless, bDMARDs work by suppressing the immune system, thereby increasing the susceptibility of infection. Also, one of components, TNF- α inhibitors, pose a risk to develop tuberculosis (TB) [6]. As a consequence, these drugs should be used under highly strict monitoring.

In addition, patients with ILD should be treated with anti-inflammatory therapy and antifibrosis therapy as soon as possible. Mycophenolate mofetil (MMF) and Rituximab (RTX) can be given to control inflammation, while nintedanib can effectively slow down the process of pulmonary fibrosis. Patients who take it everyday can slow the annual decline in lung function by about 50% [10].

4.2. Systemic Lupus Erythematosus (SLE)

Currently, in order to treat SLE, there are several therapies which should be used according to different circumstances. Some critical therapies are antimalarials, anti-inflammatory drugs and glucocorticoids (GCs). Once the diagnosis of SLE is confirmed, patients should be firstly treated with antimalarials like hydroxychloroquine (HCQ) [11]. Antimalarials can control SLE by inhibiting the intracellular toll-like receptors (TLRs). TLRs can activate immune responses. In SLE patients, TLRs may trigger fatal inflammatory reactions, damaging organs and body parts. According to some research, antimalarials are able to reduce mortality of patients by more than 50%. Also, the Toronto lupus Cohort showed that in the first 5 years, if patients use antimalarials for more than 60% of the time, the amount of flares may be reduced [12]. Based on the research, it's significant that antimalarials may reduce disease flares, mitigating damage caused by SLE. HCQ has been demonstrated that it has positive effects on treating SLE. Owing to its high lipophilicity, lysosomotropism, and pH, HCQ is able to cross cell membranes and enter lysosomes, where it suppresses NK cells and Toll-like receptors (TLRs). Additionally, it can strengthen defenses against ultraviolet (UV)-A and UV-B rays. What's more, antimalarials positively influence lipid and glucose metabolism, and they can reduce thromboembolism, as well as control cardiovascular risk. Recently, there are consensus suggestions that recommend indefinite use of HCQ therapies for SLE patients, containing patients during pregnancy [12,13]. But HCQ still have a little risk of fetal malformations. A related study found that compared to 35.3/1000 infants who were not exposed to hydroxychloroquine, approximately 54.8/1000 newborns exposed to the drug had a major congenital deformity at birth, meaning that the unadjusted relative risk was 1.51. The therapeutic benefits provided by HCQ is more than the risk, so patients should weight the advantages and disadvantages [14]. Additionally, antimalarials have inevitable side effects, such as gastric intolerance, hyperpigmentation of the skin. What's worse, they can be cardiotoxic, triggering congestive heart

failure. Nevertheless, these cases are likely to decrease after prolonged therapy [15]. In fact, it's practical to use mapacrine, the first antimalarial drug to treat lupus, to substitute for HCQ in case of side effects caused by HCQ. This method has shown a synergistic clinical advantage in SLE patients.

Other than antimalarials, GCs are also the main agents for SLE, especially in case of active disease and skin lesions. GCs work by two different ways. One of them is genomic way: transgressions and transactivation, and GCs can also work in non-genomic ways to control inflammation significantly. However, high-dose of GCs are used only when acutely indicated. Class IV GCs can be given to the scalp, palms and soles. However, other body parts should use class II and III [11]. Nonetheless, GCs should be given intermittently due to some serious side effects, such as perioral dermatitis and atrophy.

However, due to the need of long-term treatment with antimalarials and the delayed onset of antimalarials, some non-steroidal anti-inflammatory drugs or GCs can be given to achieve short-term effectiveness [11]. But if patients respond inadequately to antimalarials and GCs, or can't reduce the amount of intake of GCs <5 mg/day, it's practical to use immunosuppressants like methotrexate (MTX), azathioprine (AZA) to spare the use of GCs [13]. MTX is effective to control skin and serosal diseases, having positive effects on joints and skin lesions. AZA can target constitutional, vasculitis, haematological and neurological lupus to some extent. It can be taken in pregnancy [16].

Along with those specific medications targeting RA and SLE, it's also very critical for patients to do other supportive care. For example, they'd better control their weight, avoid excessive accumulation of fat and do adequate and proper exercise. Patients who take immunosuppressants should be vaccinated to prevent specific diseases like influenza. However, those vaccinations shouldn't contain live attenuated vaccines [11]. Furthermore, ultraviolet light protection is also necessary, and patients should give up smoking, avoid passive smoking and be protected from dust exposure.

5. Conclusion

According to this research, specific genes, excessive activation of T cells and B cells and smoking are common possible factors of both RA and SLE. Based on the fact, it's rational to make a conclusion that susceptible genes, abnormal immune responses and environmental stimulation can synergistically lead to autoimmune diseases. Some symptomatic treatments should be used to relieve symptoms. Also, symptomatic treatments like immunosuppressants are very necessary, because they are able to inhibit abnormal immune responses that target body parts by breaking the immune process. Furthermore, patients should be protected from dust and smoke, as well as ultraviolet light. Nonetheless, there are still many issues that should be solved, like multiple side effects of those therapies. So it's quite necessary to find a systematic solution to balance those side effects between different types of drugs, and invent safer drugs for women in pregnancy, or drugs with less damage to the fertility in the future. The sample size of the research in toxicity of antimalarials need to be enlarged in order to make the outcome more accurate. Apart from that, most current treatments can only control the symptoms, prevent further damage and slow down the process of developing diseases. More researches with higher evidence-based quality and larger sample sizes are needed to find out therapies that can entirely cure the AD in the future.

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