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Analysis of Autoimmune Disease: Mechanism, Genetic Susceptibility and Environmental Factors

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Abstract. This article discussed three aspects of autoimmune disease, including mechanism, genetic susceptibility, and environmental factors. Molecular mimicry and dual T cell receptor are two systems of the mechanism. Genetic susceptibility is depending on the environment and polymorphism. Lastly, the environmental factors rely on latitude, industrial development, and gender bias. This article provides a review of autoimmune disease which can help the researchers to further understand the basic information.

Keywords: Autoimmune disease (AID), Dual T cell receptors (TCR), Immune system.

1. Introduction

Chronic autoimmune disease (AID) refers to the immune system not recognizing the foreign and self-antigen correctly that the consequence is causing the inflammation and the damage of the tissue or the organ [1]. Molecular mimicry and dual T cell receptors (TCR) are the two mechanisms to explain AID, and molecular mimicry is the main and common mechanism in the disease (1). The major histocompatibility complex (MHC) in humans is the human leukocyte antigen (HLA), which is high relative to AID because it can regulate the immune system and the antigen-presenting process (2). Generally, genetic susceptibility depends on environmental and polymorphism differences [2]. There are two environmental factors relative to the AID: latitude and industrial development [3]. The latitude will influence the level of Vitamin D in the human body, and the industrial development will decrease the good infection of the immune system [3]. Furthermore, AID has gender bias and can influence by the viral factor [3]. This article will give an analysis of AID, from the perspectives of the mechanism, genetic susceptibility, and environmental factors, aiming to offer some insights and references for the future research directions of AID.

2. Mechanism

Generally, when T-cell recognizes the self-antigen as the foreign -antigen, that will cause many kinds of AID, like type-1 diabetes, systemic lupus erythematosus, and multiple sclerosis [1]. The mechanism of molecular mimicry is highly relative to these diseases both locally and systemically [1]. The molecular mimicry demonstrates that the microbial peptide has a similar sequence to the self-peptide, triggering the autoreactive T cell to mistakenly recognize the self-antigen as foreigners and cause tissue damage [1]. The T cell and tissue damage evidence are always indirect, like the cytotoxic T cell and the polymyositis [4]. The cytotoxic T cell can surround the muscle fibers and cause inflammation, and then,

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the CD8+ T cell can associate with the muscle fibers and send its "bad" molecules to the muscle fibers membrane [4]. In this way, the T cell is activated by recognizing the antigen on the muscle fiber and serves as the cytotoxic effector cell to cause the tissue damage [4]. T cell has the highly specific recognition of the receptor, and the peptide that is binding to the MHC class II to present the T cell depends on the property of the amino acid [1]. Generally, only the specific group of T cells can bind the peptide and present by MHC class II [1]. In this way, the peptide with a similar sequence can bind on the same MHC peptide, and only that specific sequence of the amino acid is needed for the TCR recognition [1].

The dual TCR is a natural product of the TCR, which has two different TCR specificities [5]. The dual TCRs allow the autoreactive T cell to escape from the thymic selection [1]. For the thymic selection of type-1 diabetes (T1D), the allelic variation and epigenetic regulation can influence the presentation of the self-epitopes on the T cell [6]. The polymorphism of the nucleotide in the insulin gene will affect the thymic expression, which refers to the thymic epithelial cells expressing different peptides to T cell, and T1D resistance is relative to transcription of the thymic gene [6]. These mechanisms will allow the autoreactive T cell to escape from the thymic selection [6]. In the human body, T1D is caused by the damage of the pancreas, which can produce insulin and cause the sugar level in the blood will increase [7-8]. Insulitis involves many factors, like the CD4+ and CD8+ T cells associated with the dysfunction of the β cell [7]. Normally, the TCR and autoreactive T cell is highly regulated, while if the T regulatory cell is not normal will cause AID [7]. The pathogenic Teff marked by the IFN-γ, and the β cell-specific type 1 CD4+ and CD8+ will expand and differentiate [7]. As a result, the autoreactive T cell will recognize the autoantigen of the β cell to cause AID [9].

3. Genetic susceptibility

HLA can affect the thymic selection and peripheral anergy of T cells in the human body, which are highly relevant to autoimmunity [2]. Spondylarthritis (SpA) is a group of inflammatory and autoimmune diseases that includes ankylosing spondylitis (AS), often associated with the HLA-B27 allele [2, 10]. The HLA-B27 can secrete the β2-microglobulin, which will deposit in the synovial tissue to cause the SpA [2]. The function of the HLA-B27 is presenting the peptide to the CD8 lymphocytes [2]. The Caucasian patient of AS has a high frequency of about 88%-96% of the HLA-B27, while in the Asian has lower [2]. This could show that genetic susceptibility relies on geographic and ethnic factors [2]. According to the research of ethnic differences, the risk of the SpA in the Caucasian group is about a 20-200-fold increase compared to the Indonesian population [2].

The different positions of amino acids, like positions 11, 71, and 74, show the polymorphism of the amino acid on the MHC class, which is a kind of method to explain the genetic susceptibility [2]. Another autoimmune disease, rheumatoid arthritis (RA), can show the strong genetic susceptibility of the HLA [2]. RA is associated with the HLA-DRB1 alleles included in the MHC class [2]. The valine at position 11 of the HLA-DRB1 can cause radiologic damage of the shared epitope [2]. Furthermore, positions 71 and 74 of the allele are relative to the erosive damage, and position 9 is the major part of the HLA of the genetic susceptibility [2]. Also, the DRB1 allele with the shared epitope can cause genetic susceptibility by selecting the self-peptide presentation [11]. DRB1*04:01 protein has a higher affinity with the citrullinated peptide than the non-citrullinated peptide [11]. Therefore, the shared epitope alleles can cause the pathogenic effect through the present citrullinated peptide, and then, the peptide will be recognized as non-self by the T cell and cause the AID [11].

Multiple sclerosis (MS) is one of AID that the female has more than twice the frequency than the male has this disease [3, 12]. The feature of MS is that dissemination of the central nervous system (CNS) will cause the lymphocytes to attach the self-antigen of the CNS [3, 13]. In detail, the dendritic cell can activate the autoreactive T cell by presenting the antigen, and the CD8+ T cell can secrete the granzyme B and perforin to damage the axon of the CNS [3]. In the high latitude and developed countries, people are easier to have MS [3]. According to the research, Vitamin D can reduce the risk of AID [14]. The human body needs to synthesize Vitamin D, and one method is exposure to sunshine [15]. While in the Northern, the sunlight is not enough, which is why there are so many people who have MS disease

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[3]. People can also obtain Vitamin D through the diet, like fatty fish, that's why people living in the coastal areas have a low risk of MS [3].

4. Environmental factors

In the early stage, if the individual is not suffering the infection, it will be easier to get the AID because he doesn't have a robust immune system against the pathogen [3]. Some infectious agents can protect the human body, but some are not, like the Epstein-Barr virus (EBV), which can cause MS, especially in adolescence [3]. One reason may be that the EBV has a similar structure with the EBV nuclear antigen; thus, the wrong recognition with the T cell may occur [3]. In contrast, the parasitic worms in the gastrointestinal tract (GIT) are an excellent infection because they can provide an anti-inflammatory function [3]. As a result, in the industrialized countries, the decrease of the colonization of parasitic worms in the GIT is associated with the high risk of MS [3].

Currently, the AID treatment is ineffective, like most of the drugs are non-specific to the disease [16-17]. One of the biological drugs to treat RA is the TNF (tumor necrosis factor) inhibitor, which will trigger severe side effects, and as time goes by self-tolerance leads the drug no longer helpful [16]. In addition, systemic sclerosis is an inheritance AID by HLA [18]. Therefore, using the HLA is an effective method to diagnose the disease, but the high polymorphism of the gene is difficult to control which means that it is difficult to use in the clinical field [3].

In the future, people may focus on one perspective disease to develop a treatment method [16]. The new drug may base on each patient's molecular and clinical features to reduce the side effects and increase efficiency [16, 19]. Furthermore, genome-wide association studies may be the major field for scientists to dig into the immune system of humans, which can further help the clinal diagnosis [16].

5. Conclusion

In conclusion, the article analyzes AID's mechanism, genetic susceptibility, and environmental factors. Through the mechanism, we can know that the T cell can recognize self-antigen as the foreign antigens which will trigger the tissue damage and cause the disease. Furthermore, the HLA allele is highly associated with the disease, like the RA is relative to the HLA-DRB1 alleles, and the SpA is relative to the HLA-B27 allele. The environmental factors can influence the level of Vitamin D in the human body, which functions as anti-inflammatory action. Also, gender bias and vital factor can influence the AID. At last, losing the beneficial infection in the early stage of humans will also cause the individual easier to carry the disease.

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