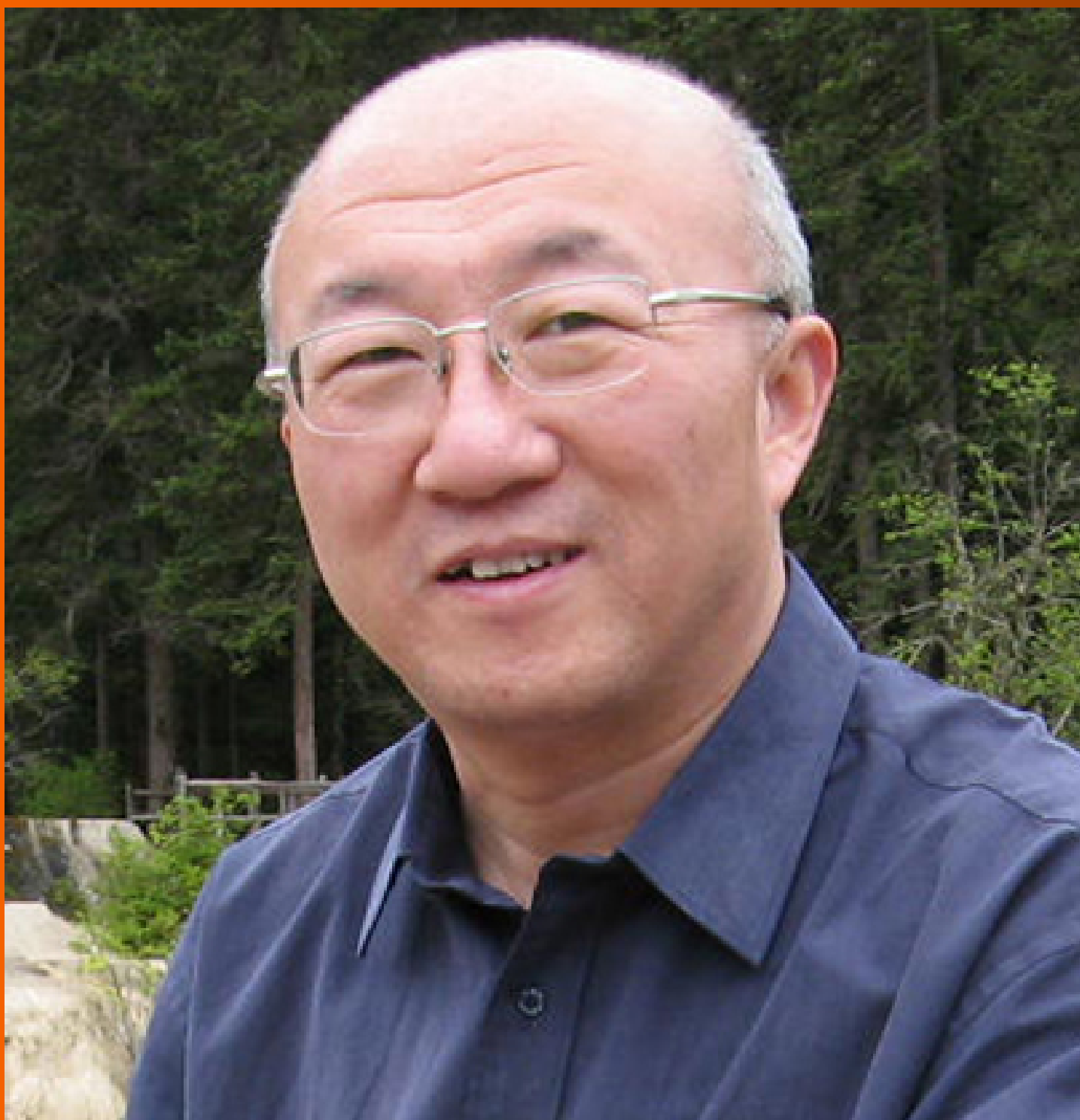


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Pathogenesis of autoimmune hepatitis

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Abstract

Autoimmune hepatitis (AIH) is a chronic progressive liver disease whose etiology and pathogenesis are not yet clear. It is currently believed that the occurrence of AIH is closely related to genetic susceptibility and immune abnormalities, and other factors such as environment, viral infection and drugs that may cause immune dysfunction. This article reviews the pathogenesis of AIH and describes the latest research results in the past 5 years.

Key Words: Autoimmune hepatitis; Genetic susceptibility; environmental factors; Immunomodulation; Drug-induced liver injury; Intestinal microbes

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Core Tip: Autoimmune hepatitis (AIH) has no specific clinical manifestations. AIH patients often require steroid hormones plus immunosuppressive maintenance therapy. Long-term medication may cause various adverse reactions, complications, and relapse after drug withdrawal, which imposes a heavy burden on patient's health and quality of life. Although the exact pathogenesis of AIH is still unclear, there are multiple theories, and continuous in-depth research on its pathogenesis has led to development in treatment of AIH. Genetic susceptibility, environmental factors (viruses, parasites, pets, etc.), immune system, drugs and biological agents, pregnancy and liver transplantation have been reported to be associated with AIH.

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INTRODUCTION

Autoimmune hepatitis (AIH) is more common in female patients. There are no specific clinical symptoms in the early stage. Serology mainly manifests as hypergammaglobulinemia and multiple autoantibodies. Histologically, a large number of plasma cells infiltrate the portal area and involve the surrounding liver parenchyma to form interface hepatitis. AIH was first proposed in 1950. Because of the similar clinical manifestations and autoantibodies between this disease and systemic lupus erythematosus, it was originally called lupus-like hepatitis. After 10 years, it was discovered that this disease had obvious differences in clinical manifestations and autoantibodies from systemic lupus erythematosus, and autoimmune liver disease and autoimmune chronic active hepatitis are collectively referred to as AIH[1]. AIH has a global distribution and can occur in men or women of any age and race. The age of onset is bimodal. The peak onset is in adolescence and middle age, especially menopausal women. At present, the clinical treatment of AIH is unsatisfactory, and with the increase of morbidity, it imposes a heavy burden on health and quality of life. Although the exact pathogenesis of AIH is still unclear, there are many theories, and the continuous in-depth research on its pathogenesis has led to development in treatment of AIH. This article summarizes recent progress of research into the pathogenesis of AIH.

GENETIC PREDISPOSITION

AIH is a polygenic disease. HLA class II DRB1 alleles are associated with AIH in different populations (Table 1). HLA-DRB1*13:01 and *03:01 alleles are related to AIH type I. In South America, AIH is mainly related to HLA-DRB1*13:01 alleles, while HLA-DRB1*03:01-negative type I AIH is mostly related to HLA-DRB1*04:01[1,2], and in Japan it is related to HLA-DRB1*04:05, *04:01, *08:02 and *08:03. It may be that the amino acid sequence in the binding region of HLA-II molecules of different races differs slightly[3]. The high frequency of HLA-DRB3*01:01 and HLA-DQB1*02:01 haploid is also related to type I AIH. In South America, HLA-DQ2 is a risk factor for AIH, and HLA-DR5 and DQ3 are protective factors for this population[4]. HLA-DRB1*04:05, HLA-DRB1*13:01, HLA-DQB1*02 and HLA-DQB1*06:03 are the main risk factors for the onset of AIH, while HLA-DRB1*13:02 and DQB1*03:01 are protective factors. These HLA molecules have P1, P4, and P6 pockets. The physicochemical acquaintances and differences of the key amino acids encoded by the peptide-binding grooves illustrate their influence on the development of disease. In Europe and Japan, HLA-DRB1*15:01 is also a protective factor[3]. HLA-DRB1*07:01, *03:01, and *02:01 alleles are associated with AIH type II. Patients with HLA-DRB1*07:01 have rapid disease progression and poor prognosis. The genetic susceptibility and severity of disease in British and Brazilian type II AIH patients are related to HLA-DRB1*03:01 alleles[1-3]. Gene mutations other than HLA are also related to AIH susceptibility or progression: Fas-670a/g and Fas-1377g/a polymorphisms[5], VDR[6], and GATA-2[7] are closely related to the onset of AIH. The high-affinity combination of y1 and -1993 c alleles inhibits expression of tbx21, which may inhibit the occurrence of AIH I by inhibiting the type 1 immune response[8]. The haplotypes of the rs7582694-c and rs7574865-t alleles in the stat4 allele are related to the increased risk of AIH I, while the rs2476601 in the ptpn22 allele is related to reduced risk of AIH I[9]. The CTLA-4 molecule is a key regulator of lymphocyte response, and ctla4a/a is a protective genotype of Tunisian patients, and the Ctla4 gene +49 polymorphism is related to AIH susceptibility. Ctla4 gene mutations may lead to changes in the structure of CTLA-4 protein, leading to onset of AIH[10]. a20 encoded by Tnfrsf25 is an inhibitor of the nuclear factor (NF)-κB signaling pathway and a susceptibility gene for autoimmune diseases. The harmful mutations of tnfrsf25 and drb1 alleles may be independently related to type I AIH, and are related to AIH and liver cirrhosis in Japan[1]. GATA2 encodes a transcription factor for hematopoietic cells, and mutations may be manifested as a reduction in monocytes, lack of dendritic cells and B cells, bone

Table 1 Susceptibility genes of autoimmune hepatitis

| Type of AIH | Susceptibility genes or alleles (protective alleles are in bold) | Country | Ref. |
|-------------|--|--|---|
| AIH I | DRB1*03:01, DRB1*04:01, DRB1*15:01 | European, North American | Higuchi <i>et al</i> [1], 2021 Higuchi <i>et al</i> [2], 2019 |
| | DRB1*04:01, DRB1*04:05, DRB1*13:02 , DRB1*15:01 , DRB1*0802, DRB1*0803 | Japanese | Higuchi <i>et al</i> [1], 2021 Higuchi <i>et al</i> [2], 2019 |
| | DRB1*0404, DRB1*0405, DRB1*1301, DRB1*1302 | Latin American | Duarte-Rey <i>et al</i> [4], 2009 |
| | DQB1*02, DQB1*0603, DQB1*0301 , DR5 , DQ3 , DQ2 | Latin American | Duarte-Rey <i>et al</i> [4], 2009 |
| | Fas-670a/g | New Zealand, China, United States, Japan | Yan <i>et al</i> [5], 2020 |
| | GATA-2 | European, Caucasian ancestry | Webb <i>et al</i> [7], 2016 |
| | TBX21-1993C | China | Sun <i>et al</i> [8], 2017 |
| | STAT4 (rs7582694-c, rs7574865-t), Ptpn22-rs2476601 | China, Japan | Li <i>et al</i> [9], 2017 |
| | CTLA4 | European, Japanese | Chaouali <i>et al</i> [10], 2018 |
| | SH2B3, VDR, FAS-1377g/a, TNFAIP3 | Japanese | Ngu <i>et al</i> [3], 2017 Yan <i>et al</i> [5], 2020 Kempinska-Podhorodecka <i>et al</i> [6], 2020 McReynolds <i>et al</i> [11], 2018 |
| | SH2B3, CARD10 | Netherlands | Motawi <i>et al</i> [13], 2019 |
| | MIF-173gc | United States, Japan | Alsayed <i>et al</i> [14], 2020 |
| | DRB1*0701, DRB1*0201 | European | Ngu <i>et al</i> [3], 2017 Duarte-Rey <i>et al</i> [4], 2009 |
| AIH II | DRB1*0301 | British and Brazilian | Ngu <i>et al</i> [3], 2017 |
| | DQB1*0201 | Latin American | Duarte-Rey <i>et al</i> [4], 2009 |

AIH: Autoimmune hepatitis.

marrow dysplasia and immunodeficiency, which are related to the pathogenesis of AIH[7,11]. HLA-DRB15 is significantly correlated with increased levels of interleukin (IL)-8. IL-6, IL-8 and tumor necrosis factor (TNF)- α may be biomarkers of AIH activity. *HLA* gene expression may play a role in the production of cytokines, and enable earlier diagnosis and better treatment[12]. Recent studies have reported that AIH I in Dutch adults is associated with mutations in the MHC region, and identified sh2b3 and card10 mutations as possible risk factors. These findings support the complex genetic basis of AIH pathogenesis and indicate partial inheritance. Susceptibility overlaps with other immune-mediated liver diseases. However, in the Japanese population, there is no connection between the card10 rs6000782 variant and AIH[13]. The Mif-173 gc polymorphism is associated with the severity of AIH in children, and may help predict the increase in serum alanine aminotransferase (ALT) levels in the early stage of onset and necrotizing inflammation/fibrosis after immunosuppressive treatment[14]. TIPE2 has a protective effect on AIH. The expression of TIPE2 in mice with AIH is significantly reduced, while the serum ALT and aspartate aminotransferase (AST) levels of TIPE2-deficient mice are significantly increased, the release of pro-inflammatory cytokines is increased, and hepatitis is more serious. It is suggested that TIPE2 alleviates liver dysfunction after AIH and inhibits harmful inflammatory immune responses, so it can be used as a new drug for the treatment of AIH[15]. Immunogenetic factors can affect the clinical manifestations of AIH in ethnic groups[3]. The prognosis of AIH patients in Asians is poor. The indigenous Alaskan population has acute jaundice hepatitis, while the Spanish ethnic group is prone to cirrhosis. HLA-DRB1*0301/*0401 also has a significant impact on the clinical manifestations of AIH. DRB1*0301-positive patients are younger and more ill. They have a poor response to

glucocorticoid treatment and are prone to relapse. It is more common to die of liver failure, and the probability of liver transplantation is high. Patients who are positive for HLA-DRB1*0401 are generally elderly women, who are relatively mildly ill, often accompanied by other autoimmune diseases, and hormone therapy is effective.

ENVIRONMENTAL FACTORS

Peptides of some viruses and hepatocyte antigens can cross-react

Since immune cross-reaction is not seen until a long time after virus infection, it is difficult to find the basis for viral infection. Common viruses include hepatitis viruses, measles virus, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus, and the most evidence is related to hepatitis viruses[16,17]. There is no difference between hepatitis E virus (HEV) seroprevalence rate in AIH patients in Catalonia and the general population. In patients with acute AIH, higher gammaglobulin levels and antibody titers, and higher HEV seropositivity indicate that there is a cross-reaction between HEV and liver antigens[17]. HEV infection may induce onset of AIH and affect its therapeutic response[16,17]. During acute HEV infection, AIH needs to be ruled out. Similarly, before diagnosis of AIH, acute HEV infection should be excluded. Immunization may also cause AIH, and influenza vaccination may trigger the development of AIH[18].

Vitamin D

Vitamin D has immunoregulatory, anti-inflammatory, antioxidative and antifibrotic effects, which may affect the occurrence and outcome of immune-mediated diseases. Macrophages and dendritic cells produce 1,25-dihydroxyvitamin D in the microenvironment, which can inhibit proliferation of immune cells, promote distribution of anti-inflammatory cytokines, expand regulatory T cells (Tregs), enhance the effect of glucocorticoids, increase production of glutathione, and inhibit hepatic stellate cells. Vitamin D deficiency usually exists in patients with immune-mediated liver disease and non-liver disease, and is related to the histological severity of AIH, advanced liver fibrosis, the ineffectiveness of conventional glucocorticoid therapy, and the need for liver transplantation[19]. Another study found that genetic variants of VDR genes (TaqI-rs731236, BsmI-rs1544410 and ApaI-rs7975232) can affect the susceptibility of individuals to chronic autoimmune liver diseases (such as AIH and primary biliary cholangitis, and affect quality of life[6].

Intestinal microenvironment and intestinal barrier

Intestinal barrier dysfunction and bacterial translocation can initiate autoimmune responses in AIH. Intestinal leakage in AIH patients is related to abnormal intestinal microbes. Damage to the intestinal barrier can cause pathogenic bacteria and their products such as lipopolysaccharide and DNA-containing unmethylated CpG to enter the liver. These gut-derived toxins may promote the signaling pathways related to liver inflammation through the abnormal activation of the innate immune system, such as activating NF- κ B, inducing activation of macrophages and releasing various pathogenic inflammatory cytokines, leading to occurrence of AIH[20-22]. Because AIH patients have impaired integrity of intestinal tight junctions, they also have intestinal flora imbalance, characterized by decrease of bifidobacteria, and changes in fecal microbes of specific diseases have been found. AIH patients may have bacterial flora migration, and intestinal barrier dysfunction and bacterial translocation are related to disease severity/increased activity[21]. Study of the changes in the composition and function of the intestinal microbiome in AIH, using the intestinal microbiota as a non-invasive biomarker, can be used to assess disease activity[22]. These results indicate that the intestinal flora provides new diagnostic methods and therapeutic targets in AIH.

Alcohol, pets and parasites

Alcohol exposure can affect the function of dendritic cells, reduce antigen presentation, and thereby inhibit the immune response. Studies have pointed out that antibiotics are an independent risk factor for the occurrence of AIH. Wood heating of households is an independent protective factor for prevention of AIH[23]. Close contact with pets (especially cats) is a risk factor for autoimmune liver disease. This finding indicates that an unknown substance (*i.e.*, toxin/microorganism) is involved in the triggering of these diseases[24]. Parasite studies have shown that soluble liver

antigen/liver pancreas (SLA/LP) protein is a highly specific diagnostic marker for AIH. The immunodominant regions of SLA/LP and rickettsial surface antigen ps120 are structurally similar, and may drive the autoimmune response mediated by CD4⁺ T lymphocytes[25].

DRUG OR BIOLOGICAL AGENT INDUCTION OF AIH

Drug-induced AIH (DIAIH) occurs in patients who have not previously been diagnosed with AIH or are susceptible to AIH. Many drugs can induce AIH, including nitrofurantoin, minocycline, hydralazine, methyldopa, indomethacin, diclofenac, atorvastatin, Tienilic acid, interferon, TNF- α , and some Chinese herbal medicines. The occurrence of DIAIH is related to gender, age, drug dose, genetic polymorphism, and drugs. Its pathogenesis is related to autoantibodies against proteins expressed in liver cells, and results from the reaction of unstable drug metabolites with cellular components. In particular, proteins in the P450 cytochrome system are considered neoantigens[26,27]. DIAIH is different from other forms of hepatotoxicity in which autoantibodies are usually negative. DIAIH has antinuclear antibodies, elevated anti-smooth muscle antibodies or gammaglobulin, and/or a specific HLA haplotype[26-28]. The difference in the incidence of DIAIH among countries may be due to population differences and the heterogeneity of the drug supply. Nitrofurantoin and minocycline are the main causes of DIAIH. Among cases of hepatotoxicity with nitrofurantoin and minocycline, DIAIH accounts for 82% and 73%, respectively. The incidence of AIH induced by methyldopa is 55%, and 43% for hydralazine. A prospective study of the Drug-induced Liver Injury Network (DILIN) showed that nitrofurantoin and nonsteroidal anti-inflammatory drugs accounted for 84% of DIAIH cases, and nitrofurantoin cases were as high as 67%[28,29]. Biological agents (*e.g.*, infliximab/adalimumab) have recently begun to constitute a cause of DIAIH, appearing in the early stage of drug withdrawal (as early as 2 mo), accompanied by short-term immunity inhibition, but there are no records of recurrence[30,31]. Diagnosis of DIAIH and AIH is difficult to distinguish. The response of DIAIH to hormone therapy is similar to that of AIH, but DIAIH has good prognosis. After discontinuation of immunosuppressive therapy, no patients have relapsed or progressed to cirrhosis or required liver transplantation. AIH has a higher degree of fibrosis than DIAIH has, and relapse can occur after drug discontinuation, with later progress to liver cirrhosis or even liver transplantation. More importantly, compared with AIH, patients with DIAIH have higher serum ALT and AST levels, more severe lobular inflammation, and higher frequency of necrosis, the number of CD4⁺ Foxp3⁺ CD25⁺/- Tregs in hepatic lobules is higher, but there is no significant difference in the frequency of peripheral blood CD4⁺ Foxp3⁺ CD25⁺/- Tregs between DIAIH and AIH [30]. An increasing number of studies have shown that drugs have some effect on AIH, but the specific pathogenesis needs further research.

ABNORMAL AUTOIMMUNE REGULATORY MECHANISM

It is currently believed that the immune response of AIH is likely initiated by the presentation of autoantigens to uncommitted naive CD4⁺ helper T (Th0) cells. CD4⁺ Th0 cells are activated in the antigen presentation process in the presence of appropriate co-stimulatory signals, and differentiate into different helper T cell populations according to the cytokine environment to which they are exposed. Th0 cells in the presence of IL-12 differentiate into Th1 cells, differentiate into Th2 in the presence of IL-4, and differentiate into Tregs or Th17 cells in the presence of TGF- β [32, 33]. Tregs and Th17 cells play an important role in the occurrence and development of immune-mediated hepatitis. Tregs include two subgroups, CD4⁺ CD25⁺ and CD8⁺. The former is the main factor in maintaining immune tolerance. The surface of Tregs can express IL-2 receptor, glucocorticoid-induced TNF receptor, Foxp3, CTLA-4, and chemokine receptors 4, 6, 7, 8 and 10. CD4⁺ CD25⁺ Foxp3⁺ Tregs inhibitory effector cells play an important role in maintaining cell homeostasis[34-36]. AIH patients have low expression of Foxp3 in peripheral blood, decreased Tregs, and decreased ability to regulate CD4⁺ and CD8⁺ effector T cell proliferation. Th17/Th22 cells in AIH peripheral circulation and liver are increased; interferon- γ , IL-17 and IL-22 levels increase; IL-17 increases release of inflammatory factors such as TNF- α and IL-6, and induces an immune inflammatory response. The imbalance between Tregs and Th1 and Th17/Th22 cells, activated macrophages, complement and natural killer cell

activation may all participate in the pathogenesis of AIH[33-36]. The IL-1 family has a proinflammatory function, and IL-33 is a ligand for receptors of IL-1 receptor-related protein ST2 (IL1RL1/ST2) and IL-1 receptor accessory protein (IL-1RaP). The interaction of IL-33 with these receptors triggers the signaling pathways related to MyD88 and NF- κ B. The interaction between IL-33 and IL1RL1/ST2 receptors regulates Th2 response, and serves as an important part of the Th1/Th17-mediated response and inflammation induced by innate immunity[37]. IL-33 and its soluble receptor ST2 play a vital role in the pathogenesis and severity of type I AIH, and may be a new target for the treatment of AIH[37,38].

PREGNANCY AND LIVER TRANSPLANTION

Patients with a past history of AIH during pregnancy have an increased risk of recurrence of AIH. The maternal immune system expands through Foxp3+ Tregs during pregnancy and guides Th2 transformation to maintain immune tolerance and immune response in the fetus to protect against invasive organisms. However, this immunotolerant state returns to Th1 dominance, leading to AIH[39,40]. Therefore, patients with elevated transaminase or immunoglobulin G (IgG) levels during pregnancy or postpartum should be alert to the possibility of secondary AIH. AIH can appear or recur after liver transplantation, and is called *de novo* AIH or recurrent AIH. AIH may occur in patients undergoing liver transplantation due to different diseases. *De novo* AIH after transplantation may be caused by an immune response to an allogeneic antigen that triggers an autoimmune response[41,42]. Recurrent AIH is associated with elevated liver enzymes and IgG before liver transplantation, lymphoplasmacytic infiltration and steroid deficiency after liver transplantation[43,44]. Although the prognosis after liver transplantation is good, AIH may still occur/relapse after transplantation, with an estimated 1-year recurrence rate of 8%-12% and 5-year recurrence rate of 36%-68%[40]. The pathogenesis of recurrent or *de novo* AIH after liver transplantation is unclear, and may be related to factors such as transplanted organs and immunosuppressive drug treatment. Early rapid diagnosis can avoid strong rejection and possible secondary liver transplantation[41-43].

SUMMARY AND OUTLOOK

AIH has no specific clinical manifestations. AIH patients often require steroid hormones plus immunosuppressive maintenance therapy. Long-term medication may lead to various adverse reactions, complications, and relapse after drug withdrawal, which imposes a heavy burden on patient's health and quality of life. The etiology of AIH has not yet been fully clarified.

CONCLUSION

Genetic susceptibility, environmental factors (viruses, parasites, pets, *etc.*), immune system, drugs and biological agents, pregnancy and liver transplantation have been reported to be associated with AIH. The pathogenesis of AIH still needs further research.

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