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Review Article

Synthesis of Recent Advances in the Immunopathogenesis of Autoimmune Hepatitis

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Abstract

Autoimmune hepatitis often progresses to cirrhosis, liver failure, and death. Its immunopathogenic mechanisms are not completely clarified; there are multiple investigations in this field, with a view to enriching knowledge and expanding therapeutic options. The present study attempts to consolidate the most recent knowledge about the immunopathogenesis of this disease. An exhaustive search of the bibliography available in SciELO and PubMed is carried out, including review articles, experimental, clinical, cohort and meta-analysis studies. Advances in the knowledge of the immunopathogenesis of autoimmune hepatitis allow a better understanding of this disease and are the reference for the design of future treatment strategies.

Keywords: *Autoimmune Hepatitis; Liver Tolerance; Antigen Presenting Cells; Lymphoid Subpopulations; Autoantibodies*

Abbreviations

HAI: Autoimmune Hepatitis; MHC: Major Histocompatibility System; HLA: Human Leukocyte Antigens; GWAS: Genome-Wide Association; TNF-α: Tumor Necrosis Factor-Alpha; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4 Molecule; AIRE: Autoimmune Regulatory Gene; APS-1: Autoimmune Polyglandular Syndrome Type 1; APC: Antigen Presenting Cells; CD: Dendritic Cells; Mo: Macrophages; KC: Kupffer Cells; LSEC: Cells Sinusoidal Endothelial Cells; HSC: Liver Stellate Cells; MHC-I: MHC Class I; MHC-II: MHC Class II; Treg: Regulatory T Lymphocytes; Th: Helper T Lymphocytes; IL- 10: Interleukin 10; TGF-β: Growth Factor Beta; TLR: Toll-Like Receptors; IL-27: Interleukin 27; IL-6: Interleukin 6; IL-1: Interleukin 1; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; EBV: Epstein-Barr Virus; IL-12: Interleukin 12; IFN-γ: Interferon Gamma; MIF: Factor Macrophage Migration; IL-17: Interleukin 17; TFR: Follicular Regulatory T Lymphocytes; ANA: Antinuclear Antibodies; SMA: Anti-Smooth Muscle Antibodies; Anti-LKM1: Microsomal Antibody Type 1 of Kidney and Liver; SLA: Soluble Liver Antigen; Antibody; LC-1: Liver Cytosol Antigen Type 1; CYP2D6: Antibody, Cytochrome P450llD6; THF: Follicular Helper T Cells; IgG: Immunoglobulin G; IL-21: Interleukin 21; GM-CSF: Granulocyte-Monocyte Colony Stimulating Factor

Introduction

Autoimmune hepatitis (HAI) is an organ-specific autoimmune disease, which frequently progresses to cirrhosis, liver failure, and death [1,2]. Its forms of presentation include: asymptomatic, subclinical disease, acute liver failure and end-stage liver disease [1,3]. Its diag-

nosis is based on scoring systems that take into account the presence of histological findings, autoantibodies, total immunoglobulin concentrations, and the absence of markers of viral hepatitis infection [2,4]. Its association with other autoimmune diseases such as: autoimmune thyroiditis, rheumatoid arthritis, systemic lupus erythematous, Sjogren syndrome and celiac disease is not uncommon [3-5]. HAI was initially defined as a condition in young, white women [1-5]. Over the years, it has established itself as an illness with a universal distribution that can affect any age and gender, regardless of ethnicity, despite the fact that the incidence and prevalence records continue to show geographic differences [2,6-8]. The annual incidence of HAI varies between 0.67 and 2.0 cases per 100,000 inhabitants and the annual prevalence ranges between 4.0 and 24.5 per 100,000 inhabitants, depending on the geographical location [4]. In the Pacific and Asia regions, a high and stable incidence is maintained, while in several European countries an increase has been reported in recent years [4]. The incidence in Latin America is variable; reports from Cuba estimate that HAI is responsible for 56.6% of autoimmune liver diseases treated at its national referral center [9], with Brazil and Colombia being the countries in the region that have studied the largest series of cases [10]. Recent hypotheses attempt to explain these differences on the basis of microbial dysbiosis secondary to high sanitation standards and the use of antimicrobials that minimize microbiological exposure [2]. The most pragmatic researchers assume these discrepancies in relation to a diagnostic sub-registry, which reinforces the interest of the scientific community in population studies [2,6,8,11]. Mortality in HAI during the first year of diagnosis is high and exceeds almost six times that of the general population; it is considered to be influenced by socioeconomic factors such as limited access to medical care [2,7,12]. The classic therapeutic management is based on the use of corticosteroids and azathioprine, either in monotherapy or in combination therapy, to which novel biological and cellular treatments have been added [4,13,14]. If left untreated, HAI offers a poor prognosis with the development of liver failure and cirrhosis [15,16]. Liver transplantation is used as a therapeutic alternative for patients in fulminant acute liver failure without a steroid response, in the same way, those cases with end-stage liver disease, accompanied or not by hepatocellular carcinoma, may also be favored with this intervention [17-19]. The pathogenesis of HAI has not been fully clarified and, like any autoimmune disease, it has a multifactorial origin influenced by genetic, immunological and environmental mechanisms. In recent years, evidence has increased about the impact of genetic predisposition on HAI [3,10,11,14,17,18,20,21]. Genes, both dependent and independent of the major histocompatibility system (MHC), which encode human leukocyte antigens (HLA), associated with the incidence and course of this disease have been identified [3,4]. These genes directly or indirectly determine modifications in the immunological processes of antigenic presentation, activation and differentiation of lymphocytes. In Caucasian patients, associations have been established between the HLA-DR3 and DR4 alleles with the predisposition to suffer HAI [3,4]. Something similar occurs in Japan for the HLA-DR4 alleles [4]. The HLA DRB1 * 1301 alleles are correlated with the susceptibility to HAI in Latin America population [3,4,10], a meta-analysis of association in HAI including studies from Mexico, Venezuela and Colombia, confirmed the DRB1 * 0405 and DRB1 * 1301, DQB1 * alleles 02 and DQB1 * 0603 as risk factors for HAI [10,21]. These genes have not only been related to predisposition, but also to the age of presentation and severity of this condition and can be considered as a cause of the reported ethnic variations [3,4,17]. Genome-wide association studies (GWAS) have identified a correspondence between HAI and non-HLA gene polymorphism that include genes encoding cytokines and costimulatory molecules such as: tumor necrosis factor-alpha (TNF-α) and the molecule cytotoxic T lymphocyte antigen 4 (CTLA-4) [3,4]. In recent years, the understanding of the immunopathogenic mechanisms based on the loss of self-tolerance to antigens expressed in liver tissue has been a topic of interest for the design of therapeutic strategies for patients with HAI [20,22,23]. Differences in clinical phenotype, severity and complications suggest that environmental factors play an essential role as triggering and evolutionary elements in the immunopathogenesis of this entity [2-5,14]. In this sense, two terms have become a constant: molecular mimicry and the intestinal microbiome, both closely related to viral infections and the use of some drugs [24,25]. The objective of this review is to summarize the most recent aspects of the immunopathogenesis of HAI.

Pathogenesis

Central tolerance and HAI

Central immune tolerance mechanisms are based on the elimination of autoreactive lymphoid clones in the generative organs of the immune system: bone marrow and thymus [2,4,20]. Particularly in the thymus, this process acquires great importance since autoreactive T cells with the capacity to recognize autoantigens expressed in non-thymic tissues are eliminated [2,4,20]. T cells interact with autoantigens expressed by the reticular epithelial cells of the thymic stroma and initiate a clonal selection process that culminates in the elimination of autoreactive T lymphocytes [2,4,7,20,26]. These autoantigens include thymic and non-thymic proteins, present in peripheral tissues whose synthesis is regulated by the transcription factor called, autoimmune regulator known as AIRE, for its acronym in English, encoded by a gene of the same name [2,7]. In the context of autoimmune liver diseases, the failure of these thymic central tolerance mechanisms is a crucial factor for the development of HAI. The AIRE gene mutation gives rise to an autoimmune disease called Autoimmune polyglandular syndrome type 1 (APS-1) that affects various organs and tissues, including the liver, causing HAI [2,3,7]. Autoimmunity towards different tissues in the same disease, as in this disease, can be explained by the existence of common autoantigens expressed in several tissues derived from the same germ layer [1,2,27].

Peripheral tolerance in liver tissue

Dual immune regulatory mechanisms develop in the liver, ensuring the maintenance of local tolerance to foreign antigens and autoantigens, and also to trigger effective immune responses in the event of invasion by a pathogen. Continuously through the portal vein, liver tissues are exposed to various antigens from commensal organisms and pathogens [2,3,20]. With the former, a symbiosis is established, while the invading microorganisms are eliminated. The liver is recognized as a highly tolerogenic organ, with a very efficient peripheral tolerance mechanism [2,3,20]. This process is dependent on the cell populations present in liver tissue. Antigen presenting cells (APC) present in the liver include several types that differ in their functionality and specialization and can be organized into two groups: conventional APCs, such as dendritic cells (DC) and macrophages (Mo), and non-conventional APCs, including Kupffer cells (KC), sinusoidal endothelial cells (LSEC), hepatic stellate cells (HSC), hepatocytes and cholangiocytes [2,4,28]. The antigen presentation process to T lymphocytes is restricted by the interaction between MHC class I (MHC-I) with the CD8 molecules of the CD8 + T lymphocyte and the MHC class II (MHC-II) with the CD4 molecules of the T lymphocyte CD4 + [3,4]. This process determines the activation and differentiation of T lymphocytes in various subpopulations. The T helper subpopulations type 1 (Th1), type 2 (Th2), type 9 (Th9), type 17 (Th17) originate from the starting point of CD4 + T lymphocytes also known as helper T or T helper (Th). type 22 (Th 22) and regulatory T (Treg) [3,4,29]. In this process, the cytokine microenvironment is critical. Interleukin 2 (IL-2) is a key cytokine in the induction of Treg patterns in the liver [2-4]. Liver Treg cells suppress responses against liver autoantigens [2-4,7,29].

Most liver DCs have a tolerogenic phenotype, characterized by low expression of Toll-like receptors (TLR), MHC-II, and costimulatory molecules (CD80/CD86) [1-4,7,14,30]. This results in poor antigenic presentation and naive T lymphocytes activation. Hepatic DCs also produce a profile of anti-inflammatory cytokines: IL-2, IL-10 and IL-27, which induce the differentiation of T lymphocytes into subpopulations of Treg cells [7,14,16,30]. KCs constitutively express the anti-inflammatory cytokines IL-10 and TGF-β that are upregulated on stress. These cytokines not only affect T cell differentiation directly but can also confer tolerogenicity on DC and other APC [2,23,30]. In an inflammatory microenvironment induced by the presence of pathogens, KCs secrete pro-inflammatory cytokines: TNF-α, IL-6 and IL-1, which promote the recruitment of granulocytes for the elimination of the microorganism, once their clearance occurs. KC pathogens release prostaglandins and anti-inflammatory cytokines: IL-10 and TGF-β, which contribute to regulatory homeostasis and return to the tolerogenic liver environment [1,6].

Breakdown in hepatic tolerance

Although the immunological factors involved in the appearance of HAI are not clearly identified. It is valid to consider that the process occurs due to the development of an immune response to liver autoantigens. Non-conventional APCs do not constitutively express MHC-II.

Damage signs, cellular stress and inflammation, induce aberrant expression of MHC-II by KC, LSEC, HSC, hepatocytes and cholangiocytes [2,7,11,28,31]. The presence of certain HLA loci in the DR and DQ regions is associated with a higher risk of HAI, such is the case of DRB1 * 13, DRB1 * 03 and DRB * 07 alleles, which increase the disease predisposition and have been identified as a predisposing factor in South American countries [4,7,21], the same happens in Asia, with the DRB1 * 0405 and DRB1 * 0401 alleles [4]. Despite this, studies in murines with selective overexpression of MHC-II in hepatocytes did not show predisposition or increase in the prevalence of HAI [31], which reinforces the idea of the multifactorial nature in the pathogenesis of this entity, which not only is sufficient with the genetic predisposition capable of inducing an increase in the expression of MHC-II in non-classical hepatic APCs, but also the microenvironment generated by the signals of damage, stress and inflammation with induction of pro-inflammatory cytokine patterns and Th1 effector responses, which are key to the breakdown of tolerance against liver autoantigens. During the immune synapse in the liver between the APCs and T lymphocytes, the transfer of fragments of the plasma membrane from the APC to the lymphocytes can occur, by the release of extracellular vesicles or by cell-cell contact, a process called trogocytosis, an event involved in the pathogenesis of various liver diseases such as HAI [20,23,31]. Fragments that can be transferred include peptide-loaded MHC-I and MHC-II complexes. What consequence does the acquisition of these complexes have for the T lymphocyte? Effector T lymphocytes that incorporate MHC-peptide complexes can act as APCs, inducing the activation of neighboring naive T lymphocytes, which are activated in the absence of costimulatory signals, leading them to a state of clonal anergy, which causes apoptosis of these cells and therefore a decrease in the number of Tregs [31,32]. The transfer of MHC molecules and MHC-peptide complexes between APC and T lymphocyte can cause an increase in immunological synapses in liver tissue and lead to the loss of peripheral tolerance mechanisms. During liver infections, the transfer of MHC-I molecules between HSC and LSEC enhances the activation of TCD8 + lymphocytes, increasing antiviral activity [31]. This exchange is bidirectional, with implications also for the APC involved in the synapse. In the case of the hepatocyte, the loss of fragments of its plasma membrane undermines its cell surface and induces necrosis of the hepatocyte [31,33].

In viral hepatitis, the transfer of membrane fragments of MHC-peptide complexes between HSCs and LSEC has been documented, which increases the activation of CD8 + T lymphocytes by cross-presentation and consequently the activated CD8 + T lymphocytes destroy infected hepatocytes [31]. This could be a non-exclusive explanation for viral liver diseases and justifies their role as triggers of HAI by molecular mimicry and cross-reactivity, between liver antigens and foreign epitopes from different viruses such as: hepatitis A virus (HAV), virus hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), Epstein - Barr virus (EBV) and herpes simplex virus [4,31]. Molecular mimicry between liver antigens and xenoantigens of the gut microbiota has been documented in experimental models of murine HAI [34-36]. Increased intestinal permeability facilitates the transition of commensal bacteria to the portal circulation, increasing the chances of cross-reactivity and the development of immune responses against hepatic autoantigens that share structural similarities with xenoantigens of the intestinal microbiota [1,4,7]. Pathognomonic changes have also been demonstrated in the composition of the intestinal microbiota in rodents with HAI [24,25,36], so that the mapping of the intestinal microbiome opens up a field of research to elucidate this factor in the pathogenesis of this entity. A human study confirmed that people with HAI without steroid treatment have a less diverse composition of the gut microbiome than the control group of healthy volunteers, reinforcing the hypothesis that the genomic diversity of the gut microbiome influences the pathogenesis of HAI [24,25]. The influence of the use of antibiotics and the type of diet on the composition of the intestinal microbiota is recognized, this being a topic of interest in the design of strategies for the management and follow-up of patients with HAI [16,24,25,37]. In this sense, in recent years the benefit of a gluten-free diet has been highlighted in the control and improvement of liver enzymes in patients with HAI [38-40]. It has been shown that patients with HAI and celiac disease, on a gluten-free regimen, have a lower tendency to relapse after the suspension of immunosuppressive treatment than the comparison groups of patients with HAI not associated with celiac disease [6,24,25,36,39,40]. The similar combination of genes that code for MHC II in HAI and celiac disease, this condition could explain that these autoimmune diseases can coexist in the same person [40], contribute to the control of HAI at the cost of changes in styles of life, promises to be a reliable therapeutic option.

Th1 differentiation is driven by IL-12. CD 8+ T cell proliferation and macrophage activation is dependent on interferon gamma (IFN-γ), IL-12 and macrophage migration factor (MIF) [16,20,30]. Th1 and Th17 cells can cause, but Treg cells suppress, autoimmune disease.

The balance between the Th17 and Treg subpopulations has been a recurring theme in the pathogenesis of various autoimmune diseases [2,3,15]. Th17 cells and Treg cells share a common signaling pathway mediated by TGF-β. However pro-inflammatory signals present during cell activation regulate the fate of these cells reciprocally. For example, in the presence of IL-6 or IL-21, naive CD4+T cells differentiate into Th17 cells; this subpopulation is pro-inflammatory and promotes the destruction of the hepatocyte [2,16,20,30]. In recent years the role of Tregs in the pathogenesis of HAI has been investigated. However, there is no consensus, as some authors have reported a liver deficit in the amount and function of this subpopulation, while others have shown a numerical and functional response in physiological range [2,30]. In this sense, the divergence of intrahepatic Treg serum levels could be related to fibrosis processes and immunosuppressive treatment [16,20,30]. The ability of Treg cells to suppress inflammatory responses is the basis for new therapeutic approaches in HAI [2,5-7,19,37]. Both IL-2 therapy and Treg transfer are promising strategies for patients with poor response to conventional immunosuppressive therapy [2,30]. During liver infectious processes, the number of unconventional T cells, NK-T and γδ T increases, these cells once activated produce inflammatory cytokines: TNF-α, granulocyte and monocyte colony stimulating factor (GM-CSF) and IL-17 in response to bacterial and viral pathogens, which breaks the tolerogenic balance and generates an efficient response [2,7,26]. Several pathogenic mechanisms of B cells have been proposed in HAIs, including the generation of autoreactive antibodies, the over-activation of B cells, the excessive production of immunoglobulins, and the activation of T cells through their role as APCs [19,41]. The antigens that are targeted by autoantibodies in HAI have been identified in most cases. However, most autoantibodies being associated with HAI have relatively low disease specificity; the presence of autoantibodies is not a requirement for the diagnosis of HAI [1,2,7,41]. Antinuclear antibodies (ANA) were the first autoantibodies to be associated with HAI. However, ANA are also found in patients with chronic hepatitis B or C, drug-induced hepatitis and in patients with non-alcoholic fatty liver disease. Antibodies against smooth muscle (SMA) have been associated with HAI, SMA can be detected in other liver diseases like ANA [4,7,16,19,26,41]. Other autoantibodies that have been identified as biomarkers include: kidney and liver microsomal antibody type 1 (anti-LKM1), soluble liver antigen antibody (SLA) and liver cytosol antigen type 1 antibodies (LC-1) antibody whose ligand is the enzyme formiminotransferase involved in folate metabolism [7,16,26,41-43]. The anti-LKM1 ligand has a hepatocyte membrane autoantigen, cytochrome P450llD6 (CYP2D6), anti-LKM-1 antibodies are considered diagnostic, if a hepatitis C virus (HCV) infection can be excluded, since reactivity to CYP2D6 has also been found in chronic hepatitis C patients [37,41], which highlights the impact of environmental factors on the genesis of HAI. The epitope similarity between foreign and own peptides explains the appearance of autoreactive lymphocyte clones; furthermore, during the course of an infection, the diversification of the lymphocyte repertoire can give rise to autoreactive clones [14,25,36,42,43]. The correlation between antibody titers and the clinical course of HAI has been a frequent research topic; associations have been found between the presence of anti SLA with the most severe clinical course and the worst prognosis of HAI [16,42]. However, there is insufficient evidence to support the regular use of these markers for the follow-up of adult patients [2,6,16,19,42].

In patients with HAI, high concentrations of activated B cells have been recorded, several factors could regulate the overactivation of B cells in HAI [4,20,26,41].

Increased concentration of subpopulations of follicular helper T cells (THF) is a common finding in the serum of patients with HAI and correlates with the concentrations of serum immunoglobulin G (IgG) and liver inflammation [16,19,20,26]. THF cells synthesize high concentrations of IL-21 that promote the activation and differentiation of B cells into antibody-secreting plasma cells. The correlation between elevated serum IL-21 levels and necroinflammatory liver activity has supported the use of this cytokine as a biomarker of liver damage in HAI [44]. In murine models, it has been concluded that blocking THFs by neutralizing IL-21 can prevent the development of HAI [7,26,36]. The imbalance between the THF subpopulations and follicular regulatory T cells (TFR) is another mechanism invoked in HAI pathogenesis [16,26,27]. TFR subpopulations suppress the reaction of the germinal center, the site where the processes of clonal expansion and differentiation of B cells occur in the lymphoid follicles, regulating the production of antibodies [4,26,41]. The findings on the hepatic immunoregulation of B cells, exerted by the THF/TFR subpopulations, mark a starting point for the design of diagnostic markers and therapeutic targets in HAI. Experimental studies in rodents have demonstrated the role of B cells as APC in the pathogenesis

of HAI, where clones of CD19 + B lymphocyte have been identified with high efficiency in the processing and presentation of antigens to T lymphocytes and an increase in the pro-inflammatory cytokines secretion [4,26,41]. These pro-inflammatory cytokines attract T cells to interact with them. Depletion of CD19 + B subpopulations correlates with decreased proinflammatory cytokine concentrations, supporting the role of B cells in the hepatic inflammatory response [4,26,41].

Conclusion

The etiology of autoimmune hepatitis is unknown. The liver is a highly tolerant organ. The pathogenesis of HAI is thought to be secondary to a failure of immune tolerance in a genetically susceptible individual leading to a T-cell mediated inflammation caused by various environmental triggers. Research in the field of HAI immunopathogenesis has allowed the development of new diagnostic and therapeutic alternatives. The greater understanding of the causal mechanisms highlights its benefit in terms of better management and follow-up of patients. There is distressed need for more knowledge on the etiology and immunopathogenesis of AIH to develop novel therapeutic interventions.

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