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Unraveling the immunological puzzle of autoimmune hepatitis: pathogenesis, genetic triggers, and future directions

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Abstract:
Autoimmune hepatitis (AIH) is a chronic immune-mediated inflammatory liver disease characterized by progressive hepatocellular injury, circulating autoantibodies, hypergammaglobulinemia, and distinctive histopathological features. Although considerable advances have been made in understanding its immunopathogenesis, the precise mechanisms responsible for the initiation and progression of AIH remain incompletely elucidated. The disease results from a complex interaction among genetic susceptibility, environmental triggers, immune dysregulation, and impaired mechanisms of peripheral tolerance. Recent studies have highlighted the pivotal roles of autoreactive $CD4^+$ and $CD8^+$ T lymphocytes, dysfunctional regulatory T cells (Tregs), activated B lymphocytes, antigen-presenting cells, pro-inflammatory cytokines, and alterations in gut microbiota in driving persistent hepatic inflammation. Genetic predisposition is primarily associated with specific human leukocyte antigen (HLA) alleles, particularly HLA-DR3 and HLA-DR4, while numerous non-HLA genes involved in immune regulation have also been implicated. Environmental factors including viral infections, medications, herbal supplements, xenobiotics, and intestinal dysbiosis may trigger disease onset through molecular mimicry, bystander activation, or epitope spreading in genetically predisposed individuals. Advances in transcriptomics, proteomics, metabolomics, and single-cell sequencing have provided novel insights into immune cell heterogeneity and cytokine signalling pathways involved in disease progression. Conventional therapy using corticosteroids and azathioprine remains highly effective for most patients; however, treatment failure, relapse, and drug intolerance continue to present significant clinical challenges. Emerging therapeutic strategies targeting specific immune pathways, including biologics, Janus kinase inhibitors, Treg-based therapies, and precision medicine approaches, offer promising future directions. This review comprehensively discusses the immunological basis of autoimmune hepatitis, emphasizing its pathogenesis, genetic determinants, environmental triggers, immunological biomarkers, and innovative therapeutic perspectives while highlighting current knowledge gaps and future research priorities.

Keywords:
Autoimmune hepatitis; Immunopathogenesis; Regulatory T cells; Autoantibodies; HLA; Cytokines; Precision medicine; Liver immunology.

1. Introduction:
Autoimmune hepatitis (AIH) is a chronic inflammatory liver disorder characterized by immune-mediated destruction of hepatocytes resulting from the breakdown of self-tolerance against hepatic antigens. The disease affects individuals of all age groups, ethnicities, and geographical regions, although women represent approximately 70–80% of diagnosed cases. If left untreated, AIH can progress to liver fibrosis, cirrhosis, hepatic failure, and ultimately death. Fortunately, early diagnosis and timely immunosuppressive therapy substantially improve patient survival and long-term prognosis (Manns et al., 2015).
The global prevalence of autoimmune hepatitis has increased steadily during the past two decades owing to improved diagnostic awareness, widespread availability of autoantibody testing, and advances in liver biopsy interpretation. Current epidemiological estimates suggest an annual incidence ranging from 1–3 cases per 100,000 population and a prevalence exceeding 20 cases per 100,000 in several developed countries. Recent

studies have also reported increasing disease incidence in Asian populations, indicating that AIH is no longer considered a predominantly Western disease (Mack et al., 2023).

Unlike viral hepatitis or alcoholic liver disease, autoimmune hepatitis develops when the host immune system mistakenly recognizes normal hepatocytes as foreign antigens. Under physiological conditions, the liver maintains a unique immunological environment that promotes immune tolerance despite continuous exposure to dietary antigens, microbial products, and circulating toxins originating from the gastrointestinal tract. This tolerogenic state is maintained through coordinated interactions among Kupffer cells, liver sinusoidal endothelial cells, dendritic cells, regulatory T cells (Tregs), and anti-inflammatory cytokines. However, disruption of these tightly regulated immune mechanisms results in persistent activation of autoreactive lymphocytes, leading to chronic hepatic inflammation (Liberal et al., 2016).

The immunopathogenesis of AIH represents one of the most complex examples of organ-specific autoimmunity. Both innate and adaptive immune responses contribute significantly to disease initiation and progression. Antigen-presenting cells activate naïve T lymphocytes following recognition of hepatic autoantigens, leading to differentiation of $CD4^+$ helper T cells into Th1 and Th17 subsets. These activated lymphocytes release pro-inflammatory cytokines including interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-21 (IL-21), which amplify inflammatory cascades and recruit additional immune cells into hepatic tissue. Simultaneously, autoreactive $CD8^+$ cytotoxic T lymphocytes directly induce hepatocyte apoptosis through perforin-granzyme pathways and Fas-Fas ligand interactions (Krawitt, 2006).

An equally important feature of autoimmune hepatitis is the impairment of immune regulatory mechanisms. Regulatory T cells, which normally suppress excessive immune activation and maintain peripheral tolerance, demonstrate reduced suppressive capacity and altered phenotypic characteristics in AIH patients. Consequently, autoreactive immune cells escape physiological control, resulting in sustained inflammatory injury. B lymphocytes further contribute by producing pathogenic autoantibodies and functioning as efficient antigen-presenting cells that perpetuate T-cell activation (Longhi et al., 2010).

Genetic susceptibility constitutes another fundamental determinant of disease development. Strong associations have been identified between AIH and several HLA class II alleles, particularly HLA-DRB1*03:01 and HLA-DRB1*04:01. These alleles influence antigen presentation and increase susceptibility to autoreactive T-cell activation. In addition, multiple non-HLA genes regulating cytokine production, immune checkpoint signalling, lymphocyte activation, and apoptosis have been implicated through genome-wide association studies. Nevertheless, genetic predisposition alone is insufficient to initiate disease, suggesting that environmental factors act as essential secondary triggers (Mieli-Vergani et al., 2018).

2. Immunology of the healthy liver:

The liver is one of the most immunologically distinctive organs in the human body because it must simultaneously perform metabolic, detoxification, and immune surveillance functions while avoiding excessive inflammatory responses. Unlike most organs, the liver continuously receives blood rich in microbial products, food-derived antigens, metabolites, toxins, and environmental molecules through the portal circulation. Under normal physiological conditions, these antigens do not provoke harmful immune activation. Instead, the hepatic immune system promotes immune tolerance while preserving the ability to mount rapid responses against genuine pathogens (Knolle & Gerken, 2000).

Approximately 80% of the liver's blood supply originates from the portal vein, which transports bacterial lipopolysaccharides, microbial DNA fragments, fungal components, dietary proteins, metabolites, and other intestinal-derived molecules directly from the gastrointestinal tract. Consequently, hepatic immune cells are exposed to an enormous antigenic load every day. Persistent inflammatory activation under these circumstances would cause extensive tissue injury; therefore, the liver has evolved highly specialized mechanisms that favour immunological tolerance over excessive immune reactivity (Jenne & Kubes, 2013).

The hepatic immune microenvironment consists of a highly coordinated network of resident and circulating immune cells. These include Kupffer cells, liver sinusoidal endothelial cells (LSECs), dendritic cells, hepatic stellate cells, natural killer (NK) cells, natural killer T (NKT) cells, regulatory T lymphocytes, B lymphocytes, macrophages, neutrophils, and infiltrating monocytes. Together, these cellular components create a finely balanced immune ecosystem capable of distinguishing harmless antigens from genuine pathogenic threats (Protzer et al., 2012).

Kupffer cells represent the largest population of tissue-resident macrophages in the human body and account for approximately 80–90% of all resident macrophages. Positioned strategically within hepatic sinusoids, Kupffer cells continuously monitor portal blood for pathogens and foreign antigens. Under physiological conditions, they predominantly exhibit an anti-inflammatory phenotype characterized by secretion of

interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), and prostaglandins. These mediators suppress excessive T-cell activation, promote regulatory T-cell differentiation, and maintain hepatic immune tolerance (Heymann & Tacke, 2016).

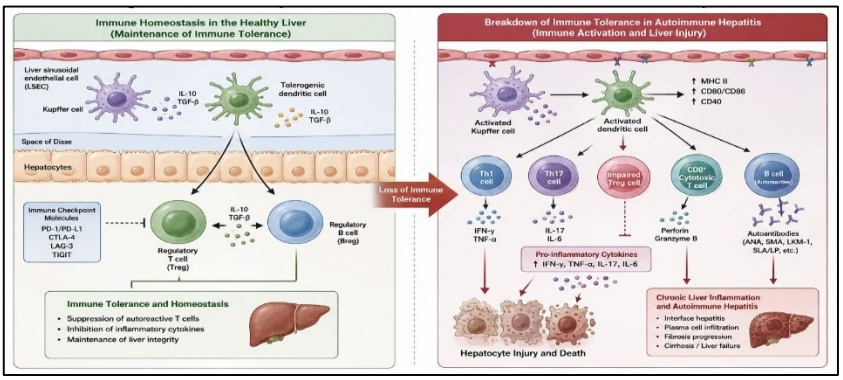

Figure. 1: Overview of Hepatic Immune Tolerance and Its Breakdown in Autoimmune Hepatitis

3. Pathogenesis of autoimmune hepatitis:

Autoimmune hepatitis develops through a multifactorial process involving genetic susceptibility, environmental exposure, and progressive dysregulation of both innate and adaptive immune responses. Rather than resulting from a single pathogenic event, AIH reflects the cumulative failure of multiple immune tolerance mechanisms that normally protect hepatic tissues from self-directed immune attack. The disease is therefore considered a prototypical example of organ-specific autoimmune inflammation, in which persistent activation of autoreactive lymphocytes drives chronic hepatocellular injury (Liberal et al., 2016).

The earliest stage of disease is believed to involve a genetically susceptible individual encountering one or more environmental triggers capable of activating innate immune pathways. Viral infections, medications, toxins, alterations in gut microbiota, and other external stimuli induce hepatocellular stress or injury, leading to the release of intracellular hepatic antigens. These self-antigens are subsequently captured by dendritic cells, Kupffer cells, and other antigen-presenting cells, initiating activation of autoreactive T lymphocytes within hepatic lymphoid tissues (Mieli-Vergani et al., 2018).

Under normal physiological conditions, presentation of hepatic self-antigens induces immune tolerance rather than immune activation. However, in genetically predisposed individuals, defects in antigen presentation, impaired regulatory T-cell function, abnormal cytokine signalling, and altered co-stimulatory pathways allow autoreactive T cells to escape immune regulation. These activated lymphocytes proliferate, migrate into hepatic tissue, and initiate chronic inflammatory responses that progressively damage hepatocytes (Mack et al., 2023).

Once immune tolerance has been lost, the inflammatory response becomes self-perpetuating. Activated $CD4^+$ helper T cells stimulate macrophages, recruit neutrophils, activate B cells, and enhance differentiation of cytotoxic $CD8^+$ T lymphocytes. These immune cells release numerous inflammatory mediators that amplify hepatic injury and maintain chronic inflammation even after the initial triggering event has disappeared. Over time, repeated cycles of hepatocyte injury and regeneration promote fibrosis, architectural distortion, and eventual cirrhosis if effective immunosuppressive therapy is not initiated (European Association for the Study of the Liver, 2015).

3.1. Role of innate immunity in disease initiation:

Innate immunity constitutes the first line of defence against pathogens and plays a pivotal role in initiating the inflammatory cascade that ultimately culminates in autoimmune hepatitis. Although AIH is classically regarded as an adaptive immune-mediated disorder, increasing evidence suggests that abnormalities in innate immune activation precede and facilitate autoreactive T-cell responses. Hepatocyte injury caused by infections, drugs, toxins, or oxidative stress results in the release of damage-associated molecular patterns (DAMPs), including high mobility group box-1 (HMGB1), heat shock proteins, mitochondrial DNA, ATP, and nuclear proteins. These endogenous danger signals are recognized by pattern-recognition receptors (PRRs) expressed on Kupffer cells, dendritic cells, macrophages, and liver sinusoidal endothelial cells, thereby initiating sterile hepatic inflammation (Kubes & Jenne, 2018).

Among PRRs, Toll-like receptors (TLRs) have received particular attention in AIH. TLR2, TLR4, TLR7, and TLR9 recognize microbial and endogenous ligands, activating downstream signalling pathways mediated by myeloid differentiation factor 88 (MyD88) and nuclear factor-kappa B (NF-κB). Activation of these pathways induces transcription of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α),

interleukin-1β (IL-1β), IL-6, and IL-12, creating an inflammatory microenvironment that promotes activation of adaptive immune responses. Persistent stimulation of TLR signalling has been associated with disease severity and progression in autoimmune liver disorders (Albillos et al., 2020).

3.2. Adaptive immunity: the central driver of autoimmune hepatitis:

Although innate immunity initiates hepatic inflammation, adaptive immune responses are primarily responsible for sustaining chronic autoimmune injury. The hallmark of AIH is the expansion of autoreactive T and B lymphocytes directed against hepatic self-antigens. Failure of central and peripheral tolerance mechanisms permits these autoreactive lymphocytes to survive, proliferate, and infiltrate liver tissue, where they orchestrate progressive hepatocyte destruction (Liberal et al., 2016).

Activation of adaptive immunity begins when dendritic cells present hepatic autoantigens to naïve $CD4^+$ T lymphocytes through MHC class II molecules. Successful T-cell activation requires both antigen recognition and co-stimulatory signalling via CD80/CD86-CD28 interactions. Once activated, naïve T cells differentiate into distinct effector subsets according to the surrounding cytokine environment. In AIH, differentiation is strongly biased toward Th1 and Th17 phenotypes, whereas regulatory T-cell development is impaired, resulting in a profound imbalance between inflammatory and immunosuppressive immune pathways (Sakaguchi et al., 2020).

3.3. Th1-mediated immune responses:

Th1 cells play a dominant role in autoimmune hepatitis by promoting cell-mediated immunity. Differentiation of naïve T cells into Th1 lymphocytes is driven primarily by IL-12 produced by activated dendritic cells and macrophages. Mature Th1 cells secrete IFN-γ, TNF-α, and IL-2, cytokines that activate macrophages, enhance antigen presentation, stimulate cytotoxic T-cell responses, and amplify inflammatory signalling. IFN-γ also increases expression of MHC class I and II molecules on hepatocytes, rendering them more susceptible to immune-mediated attack (Mieli-Vergani et al., 2018).

TNF-α contributes directly to hepatocyte apoptosis through activation of TNF receptor signalling pathways while simultaneously promoting recruitment of additional inflammatory leukocytes. Elevated serum concentrations of TNF-α and IFN-γ correlate positively with biochemical disease activity and histological severity in AIH patients, emphasizing the importance of Th1-mediated inflammation in disease progression (Liberal et al., 2016).

3.4. Th17 cells and chronic inflammation:

Over the past decade, Th17 lymphocytes have emerged as another critical mediator of autoimmune hepatitis. Differentiation of Th17 cells is promoted by IL-6, IL-1β, TGF-β, and IL-23. Once activated, Th17 cells produce IL-17A, IL-17F, IL-21, and IL-22, cytokines that recruit neutrophils, stimulate fibroblasts, activate hepatic stellate cells, and enhance production of inflammatory chemokines (Korn et al., 2009).

IL-17 promotes expression of CXCL1, CXCL8, granulocyte colony-stimulating factor (G-CSF), and matrix metalloproteinases, thereby amplifying neutrophil recruitment and tissue injury. Furthermore, IL-17 stimulates hepatic stellate cells to synthesize collagen and extracellular matrix proteins, contributing to liver fibrosis during chronic disease. Clinical studies consistently demonstrate increased circulating Th17 cells and elevated serum IL-17 concentrations in patients with active autoimmune hepatitis, supporting their pathogenic role (Longhi et al., 2010).

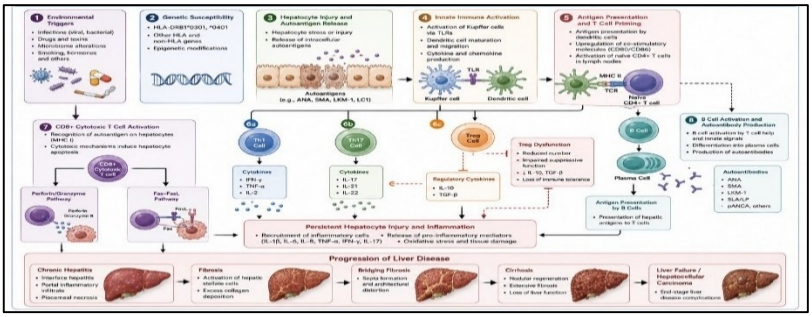

Figure.2: Immunopathogenesis of Autoimmune Hepatitis

3.5. $CD8^+$ cytotoxic t lymphocytes: direct mediators of hepatocyte injury:

While $CD4^+$ T helper cells coordinate immune responses, $CD8^+$ cytotoxic T lymphocytes (CTLs) are primarily responsible for the direct destruction of hepatocytes in autoimmune hepatitis. Numerous histopathological

studies have demonstrated dense infiltration of activated $CD8^+$ T cells within portal tracts and hepatic lobules, particularly at the interface between portal connective tissue and hepatic parenchyma. The abundance of these cells correlates closely with biochemical disease activity and histological severity, suggesting that CTLs are major effector cells responsible for ongoing liver injury (Liberal et al., 2016).

Activation of $CD8^+$ T cells occurs following recognition of hepatic autoantigens presented by major histocompatibility complex class I (MHC-I) molecules expressed on hepatocytes and antigen-presenting cells. Once activated, CTLs undergo clonal expansion and migrate into hepatic tissue under the influence of chemokines such as CXCL9, CXCL10, and CCL5. These chemokines are predominantly induced by interferon-gamma (IFN-γ), thereby establishing a positive feedback loop that continuously recruits additional inflammatory lymphocytes into the liver (Mieli-Vergani et al., 2018).

3.6. B lymphocytes and autoantibody production:

Although T lymphocytes are considered the principal drivers of autoimmune hepatitis, B cells play equally important roles in disease pathogenesis through antibody production, antigen presentation, and cytokine secretion. Activated B cells differentiate into plasma cells that produce characteristic circulating autoantibodies, one of the defining diagnostic features of AIH (Longhi et al., 2010).

The most frequently detected autoantibodies include antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), anti-liver kidney microsomal type 1 antibodies (anti-LKM-1), anti-liver cytosol type 1 antibodies (anti-LC1), and antibodies against soluble liver antigen/liver pancreas antigen (anti-SLA/LP). Although these autoantibodies are valuable diagnostic biomarkers, accumulating evidence suggests that they also contribute directly to disease pathogenesis by forming immune complexes, activating complement pathways, and facilitating antigen uptake by dendritic cells and macrophages (Manns et al., 2015).

Beyond antibody production, B lymphocytes function as highly efficient antigen-presenting cells. Following uptake of hepatic autoantigens through B-cell receptors, these antigens are processed and presented to $CD4^+$ helper T cells via MHC-II molecules. Activated helper T cells subsequently provide co-stimulatory signals through CD40-CD40L interactions, promoting further B-cell proliferation, plasma-cell differentiation, and antibody production. This reciprocal activation between T and B cells establishes a self-perpetuating cycle of chronic autoimmune inflammation (Liberal et al., 2016).

3.7. Regulatory T-Cell dysfunction: breakdown of peripheral immune tolerance:

Maintenance of self-tolerance depends largely upon regulatory T cells (Tregs), specialized $CD4^+CD25^+FOXP3^+$ lymphocytes that suppress excessive immune activation. Under physiological conditions, Tregs inhibit autoreactive T cells through secretion of IL-10, TGF-β, and IL-35, competition for IL-2, expression of inhibitory molecules such as CTLA-4, and direct suppression of antigen-presenting cells. These mechanisms collectively prevent immune responses against self-antigens and preserve tissue integrity (Sakaguchi et al., 2020).

One of the most consistent immunological abnormalities identified in autoimmune hepatitis is quantitative and functional impairment of Tregs. Several studies have demonstrated reduced frequencies of circulating $FOXP3^+$ Tregs together with diminished suppressive capacity. Consequently, autoreactive $CD4^+$ and $CD8^+$ T cells escape immune regulation, proliferate excessively, and infiltrate hepatic tissue, resulting in persistent inflammation (Longhi et al., 2010).

3.8. Cytokine networks in autoimmune hepatitis:

Cytokines orchestrate communication among innate and adaptive immune cells and are central to the pathogenesis of autoimmune hepatitis. Active disease is characterized by a profound imbalance between pro-inflammatory and anti-inflammatory cytokines, resulting in sustained activation of immune cells and progressive liver injury (Liberal et al., 2016).

Among pro-inflammatory cytokines, IFN-γ represents a major mediator of hepatic inflammation. Produced predominantly by Th1 cells, NK cells, and $CD8^+$ T lymphocytes, IFN-γ enhances antigen presentation by increasing MHC expression on hepatocytes and activates macrophages to produce additional inflammatory mediators. Elevated serum IFN-γ concentrations correlate with disease severity and histological inflammation (Mieli-Vergani et al., 2018).

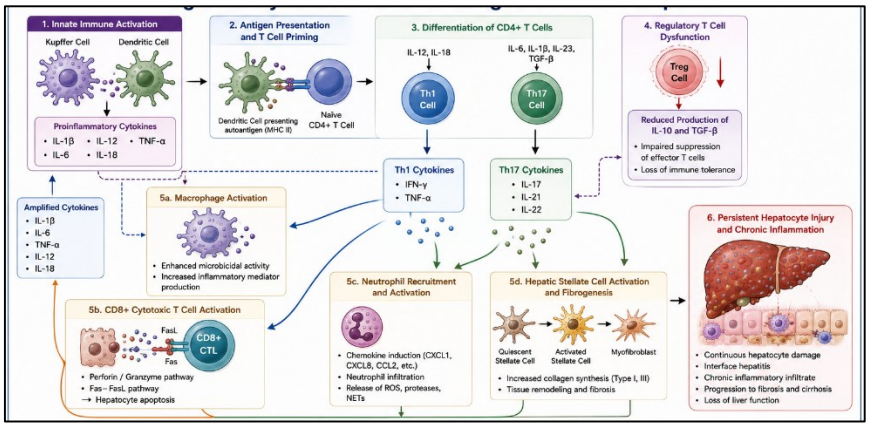

Figure.3: Cytokine Network Driving Autoimmune Hepatitis

3.9. Immune checkpoint pathways: failure of immune regulation in autoimmune hepatitis:

The immune system possesses several inhibitory mechanisms, collectively known as **immune checkpoints**, that prevent excessive immune activation and maintain self-tolerance. These regulatory pathways are essential for terminating immune responses after pathogen clearance and preventing autoreactive lymphocytes from attacking healthy tissues. In autoimmune hepatitis (AIH), accumulating evidence indicates that defects in immune checkpoint signalling contribute significantly to persistent activation of autoreactive T cells and chronic liver inflammation (Sharpe & Pauken, 2018).

Among the best-characterized checkpoint molecules are cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) **and** programmed cell death protein-1 (PD-1)**.** CTLA-4 is expressed primarily on activated T cells and regulatory T cells (Tregs), where it competes with the co-stimulatory receptor CD28 for binding to CD80 and CD86 molecules on antigen-presenting cells. Unlike CD28, CTLA-4 delivers inhibitory signals that reduce T-cell proliferation, cytokine secretion, and survival. Functional impairment or reduced expression of CTLA-4 has been associated with several autoimmune diseases, including AIH, allowing autoreactive T cells to escape normal regulatory control (Walker & Sansom, 2015).

Similarly, the PD-1/PD-L1 pathway serves as a crucial inhibitory mechanism within peripheral tissues. PD-1 is expressed on activated T lymphocytes, while its ligand PD-L1 is present on hepatocytes, Kupffer cells, dendritic cells, and liver sinusoidal endothelial cells. Engagement of PD-1 by PD-L1 suppresses T-cell receptor signalling, decreases cytokine production, and promotes immune tolerance. Reduced PD-1 signalling or impaired PD-L1 expression has been reported in patients with autoimmune liver diseases, contributing to sustained activation of inflammatory lymphocytes (Keir et al., 2008).

4. Genetic susceptibility in autoimmune hepatitis:

Although environmental triggers initiate disease onset, autoimmune hepatitis develops only in a small proportion of exposed individuals, indicating that **genetic susceptibility** plays a fundamental role in disease pathogenesis. Family clustering, concordance among monozygotic twins, and strong associations with specific immune-regulatory genes support the importance of inherited factors in determining disease risk (Manns et al., 2015).

4.1 Human leukocyte antigen (HLA) genes:

The strongest genetic associations in AIH involve the human leukocyte antigen (HLA) region located on chromosome 6. HLA molecules are responsible for presenting peptide antigens to T lymphocytes and therefore play a central role in immune recognition.

Among Caucasian populations, HLA-DRB1*03:01 (HLA-DR3) **and** HLA-DRB1*04:01 (HLA-DR4) are consistently associated with increased susceptibility to type 1 autoimmune hepatitis. Patients carrying HLA-DR3 frequently develop disease at a younger age, exhibit more aggressive clinical courses, and experience higher relapse rates following treatment withdrawal. In contrast, HLA-DR4-positive patients generally present later in life and often respond more favourably to immunosuppressive therapy (Mieli-Vergani et al., 2018).

The distribution of HLA alleles varies substantially among different ethnic populations. For example, HLA-DRB1*04 predominates in East Asian countries including Japan, whereas HLA-DRB1*13* has been associated with disease susceptibility in South America. These geographical differences suggest that population-specific genetic backgrounds influence disease risk and clinical phenotype (Mack et al., 2023).

4.2. Non-HLA susceptibility genes:

Although HLA genes account for a substantial proportion of inherited risk, numerous **non-HLA genes** involved in immune regulation also contribute to AIH susceptibility. Genome-wide association studies (GWAS) and candidate gene analyses have identified polymorphisms affecting cytokine production, lymphocyte activation, apoptosis, and immune checkpoint signalling (de Boer et al., 2014).

Variants within the **CTLA4** gene reduce inhibitory signalling and impair suppression of autoreactive T cells. Similarly, polymorphisms affecting **PDCD1**, which encodes PD-1, may weaken peripheral immune tolerance and facilitate chronic hepatic inflammation.

4.3. Epigenetic regulation:

Recent studies indicate that **epigenetic modifications** also influence autoimmune hepatitis development. Unlike genetic mutations, epigenetic changes alter gene expression without modifying DNA sequence and include DNA methylation, histone modifications, and non-coding RNAs such as microRNAs (miRNAs) (Ballestar, 2011).

Aberrant DNA methylation has been identified in genes regulating immune tolerance, cytokine production, and T-cell differentiation. Hypomethylation of inflammatory genes enhances cytokine expression, whereas hypermethylation of immunoregulatory genes may impair Treg development.

5. Environmental triggers of autoimmune hepatitis:

Genetic susceptibility alone is insufficient to produce autoimmune hepatitis. Most genetically predisposed individuals never develop disease, indicating that **environmental factors** are required to initiate the autoimmune process. These triggers induce hepatocyte injury, activate innate immune pathways, and expose hepatic autoantigens to the adaptive immune system (Tanaka, 2020).

5.1. Viral infections:

Numerous viral infections have been implicated as potential initiators of AIH. Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have all been reported to precede disease onset in susceptible individuals.

Several mechanisms have been proposed. Viral proteins may share structural similarities with hepatic self-antigens, a phenomenon known as **molecular mimicry**, resulting in cross-reactive T-cell responses. Alternatively, viral infections may induce **bystander activation**, in which inflammatory cytokines activate autoreactive lymphocytes independently of antigen specificity. Persistent viral infection may also expose previously hidden intracellular hepatic antigens through hepatocyte destruction, thereby initiating autoimmune responses (Oldstone, 2005).

Although definitive causal relationships remain difficult to establish, viral infections are widely considered important environmental contributors to AIH development.

Table.1: Major Autoantibodies in Autoimmune Hepatitis

Autoantibody	Target Antigen	Clinical Association	Diagnostic Importance
ANA	Nuclear antigens	Type 1 AIH	Common screening marker
SMA	Actin cytoskeleton	Type 1 AIH	High diagnostic value
Anti-LKM-1	CYP2D6 enzyme	Type 2 AIH	Highly specific
Anti-LC1	Formiminotransferase cyclodeaminase	Type 2 AIH	Supports diagnosis
Anti-SLA/LP	Soluble liver antigen	Severe AIH	Highly specific prognostic marker

5.2. Drugs, herbal products, and xenobiotics:

In addition to infectious agents, numerous **drugs, herbal preparations, and environmental xenobiotics** have been implicated as potential triggers of autoimmune hepatitis (AIH). Drug-induced autoimmune hepatitis (DIAIH) is a well-recognized clinical entity that closely resembles idiopathic AIH in terms of clinical presentation, biochemical abnormalities, autoantibody profiles, and histopathological findings. However, unlike classical AIH, withdrawal of the offending agent may result in sustained remission in some patients (Björnsson et al., 2010).

Several medications have been consistently associated with AIH-like syndromes, including minocycline, nitrofurantoin, methyldopa, hydralazine, interferon-α, infliximab, atorvastatin, diclofenac, and certain immune

checkpoint inhibitors. These drugs may alter immune tolerance through multiple mechanisms, including direct hepatocyte injury, formation of reactive drug metabolites, modification of hepatic proteins, and activation of autoreactive lymphocytes (European Association for the Study of the Liver, 2015).
Drug metabolites may bind covalently to hepatic proteins, forming **neoantigens** that are recognized as foreign by the immune system. These neoantigens are processed by antigen-presenting cells and presented to $CD4^+$ and $CD8^+$ T lymphocytes, initiating adaptive immune responses. Once immune tolerance has been disrupted, the inflammatory process may persist even after the offending drug has been eliminated, particularly in genetically susceptible individuals (Manns et al., 2015).

5.3. Gut microbiota and the gut–liver axis:

One of the most rapidly expanding areas of AIH research concerns the **gut–liver axis**, a bidirectional communication network linking intestinal microbiota with hepatic immune regulation. Because approximately 70–80% of hepatic blood supply originates from the portal vein, the liver is continuously exposed to microbial metabolites, bacterial components, dietary antigens, and immune mediators derived from the gastrointestinal tract. Consequently, alterations in gut microbial composition may profoundly influence hepatic immune homeostasis (Albillos et al., 2020).
The healthy intestinal microbiota contributes to immune tolerance by producing short-chain fatty acids (SCFAs), maintaining epithelial barrier integrity, promoting differentiation of regulatory T cells, and suppressing inflammatory signalling pathways. Dysbiosis, defined as an imbalance in microbial composition, disrupts these protective mechanisms and has been implicated in the pathogenesis of numerous autoimmune diseases, including autoimmune hepatitis (Tilg et al., 2022).
Patients with AIH frequently exhibit reduced microbial diversity together with depletion of beneficial bacterial genera such as **Bifidobacterium**, **Faecalibacterium**, and **Lactobacillus**, accompanied by increased abundance of potentially pathogenic organisms including **Enterococcus**, **Veillonella**, and **Streptococcus** species. These microbial alterations promote intestinal permeability, allowing bacterial lipopolysaccharide (LPS), peptidoglycans, and microbial DNA to enter the portal circulation (Wei et al., 2020).

5.4. Molecular mimicry, bystander activation, and epitope spreading:

The precise mechanism by which environmental factors initiate autoimmune hepatitis remains incompletely understood. Three complementary immunological theories have received the greatest experimental support: **molecular mimicry**, **bystander activation**, and **epitope spreading** (Oldstone, 2005).

5.1.1. Molecular Mimicry:

Molecular mimicry occurs when microbial or drug-derived antigens share structural similarities with hepatic self-proteins. Immune responses directed against infectious agents inadvertently cross-react with homologous hepatic antigens, leading to activation of autoreactive T and B lymphocytes. Numerous viral proteins exhibit sequence homology with liver proteins, providing a plausible explanation for post-infectious autoimmune hepatitis (Cusick et al., 2012).

5.1.2. Bystander Activation:

During infections or tissue injury, inflammatory cytokines including IL-1β, IL-6, TNF-α, and IFN-γ create an environment that activates nearby lymphocytes irrespective of antigen specificity. Previously quiescent autoreactive T cells may therefore become activated simply because of the surrounding inflammatory milieu, subsequently recognizing hepatic autoantigens and initiating chronic autoimmune responses.

5.1.3. Epitope Spreading:

Initially, immune responses may target only a limited number of hepatic antigens. However, ongoing hepatocyte destruction releases additional intracellular proteins, exposing previously hidden epitopes to the immune system. This progressive diversification of antigen recognition, termed **epitope spreading**, broadens the autoimmune response and contributes to chronic disease progression despite elimination of the original triggering stimulus (Lehmann et al., 1992).
These three mechanisms likely interact rather than operate independently, collectively explaining how transient environmental exposures can initiate persistent autoimmune liver disease.

6. Histopathological features of autoimmune hepatitis:

Liver biopsy remains an indispensable diagnostic tool for autoimmune hepatitis because histopathological examination provides valuable information regarding disease activity, fibrosis stage, differential diagnosis,

and therapeutic response. Although no single microscopic feature is pathognomonic, several characteristic findings strongly support the diagnosis when interpreted alongside clinical and serological data (European Association for the Study of the Liver, 2015).

The hallmark histological lesion is **interface hepatitis**, previously known as piecemeal necrosis. This lesion is characterized by dense inflammatory infiltrates extending from portal tracts into adjacent hepatic parenchyma, disrupting the limiting plate and causing hepatocyte injury. Interface hepatitis reflects active immune-mediated destruction of periportal hepatocytes and is considered the defining pathological feature of AIH (Manns et al., 2015).

Table. 2: Characteristic Histopathological Features of Autoimmune Hepatitis

Histopathological Feature	Description	Clinical Significance
Interface hepatitis	Inflammation extending from portal tract into hepatic parenchyma	Hallmark lesion of AIH
Plasma cell infiltration	Dense portal plasma-cell infiltrates	Strongly supports diagnosis
Hepatocyte rosettes	Regenerating hepatocytes arranged in gland-like structures	Indicates regenerative activity
Emperipolesis	Lymphocytes penetrating viable hepatocytes	Suggestive of active immune injury
Bridging necrosis	Confluent hepatocyte necrosis between portal areas	Indicates severe disease
Fibrosis/Cirrhosis	Collagen deposition and architectural distortion	Predictor of long-term prognosis

7. Diagnostic biomarkers and clinical evaluation of autoimmune hepatitis:

Early diagnosis of autoimmune hepatitis (AIH) is essential because prompt initiation of immunosuppressive therapy can prevent progressive liver injury, fibrosis, cirrhosis, and liver failure. However, diagnosis remains challenging because no single laboratory test is pathognomonic. Instead, AIH is diagnosed through a combination of **clinical presentation, biochemical findings, immunological markers, liver histopathology, exclusion of alternative liver diseases, and standardized diagnostic scoring systems** (European Association for the Study of the Liver, 2015).

Patients may present with a broad spectrum of clinical manifestations ranging from asymptomatic elevation of liver enzymes to acute hepatitis, chronic liver disease, or fulminant hepatic failure. Common symptoms include fatigue, malaise, anorexia, nausea, right upper quadrant discomfort, arthralgia, jaundice, pruritus, and hepatomegaly. Because these symptoms are nonspecific, laboratory investigations play a pivotal role in raising clinical suspicion (Manns et al., 2015).

7.1. Biochemical Markers:

The most frequent biochemical abnormality is **elevation of serum aminotransferases**, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), reflecting hepatocellular injury. Serum ALT levels may exceed ten times the upper limit of normal in active disease. Alkaline phosphatase (ALP) is usually normal or only mildly elevated, distinguishing AIH from cholestatic liver diseases such as primary biliary cholangitis and primary sclerosing cholangitis (European Association for the Study of the Liver, 2015).

Hyperbilirubinaemia is common in patients with severe or advanced disease, while hypoalbuminaemia and prolonged prothrombin time may indicate impaired hepatic synthetic function. Persistently elevated aminotransferases despite treatment often suggest ongoing inflammatory activity or incomplete remission.

One of the most characteristic laboratory findings in AIH is **polyclonal hypergammaglobulinaemia**, particularly elevated serum immunoglobulin G (IgG). Increased IgG reflects chronic activation of B lymphocytes and plasma cells and is present in approximately 80–90% of untreated patients. Serum IgG concentrations correlate with disease activity and frequently normalize following successful immunosuppressive therapy, making them useful for monitoring treatment response (Mack et al., 2023).

7.2. Autoantibodies:

Circulating autoantibodies constitute one of the defining immunological features of autoimmune hepatitis and provide valuable diagnostic information. However, no autoantibody is entirely specific for AIH, and results should always be interpreted in conjunction with clinical, biochemical, and histological findings.

7.3. Antinuclear Antibodies (ANA):

ANA is the most commonly detected autoantibody in **Type 1 AIH**, occurring in approximately 60–80% of patients. ANA recognizes various nuclear proteins and is detected using indirect immunofluorescence. Although ANA lacks disease specificity because it is also observed in systemic lupus erythematosus, rheumatoid arthritis, and even healthy individuals, high titres strongly support the diagnosis when accompanied by compatible clinical findings (Manns et al., 2015).

7.4. Anti-Smooth Muscle Antibodies (SMA):

SMA targets cytoskeletal proteins, particularly filamentous actin (F-actin), and is detected in nearly 70% of Type 1 AIH patients. SMA positivity, especially when combined with ANA positivity, substantially increases diagnostic confidence.

7.5. Anti-Liver Kidney Microsomal Type 1 (Anti-LKM-1):

Anti-LKM-1 antibodies recognize cytochrome P450 2D6 (CYP2D6) and are characteristic of **Type 2 AIH**, which predominantly affects children and young adults. Although less common than Type 1 AIH, Type 2 disease often follows a more aggressive clinical course and exhibits higher relapse rates.

7.6. Anti-Liver Cytosol Type 1 (Anti-LC1):

Anti-LC1 antibodies recognize formiminotransferase cyclodeaminase and frequently coexist with anti-LKM-1 antibodies. Their presence strengthens the diagnosis of Type 2 AIH and may identify patients with more severe disease.

7.7. Anti-Soluble Liver Antigen/Liver Pancreas (Anti-SLA/LP):

Among currently available autoantibodies, anti-SLA/LP exhibits the highest disease specificity. It is detected in approximately 20–30% of AIH patients and is associated with severe disease, increased relapse risk, and poorer long-term prognosis. Because anti-SLA/LP may occur even in ANA-negative patients, testing for this antibody improves diagnostic sensitivity (Liberal et al., 2016).

7.8. Emerging biomarkers:

Although conventional autoantibodies remain central to diagnosis, considerable effort has been directed toward identifying novel biomarkers capable of improving diagnostic accuracy and predicting therapeutic response.

7.9. Cytokine biomarkers:

Active autoimmune hepatitis is characterized by elevated circulating concentrations of IL-17, IL-21, TNF-α, IFN-γ, IL-6, and CXCL10. These cytokines reflect ongoing immune activation and may correlate with disease severity. Conversely, reduced IL-10 concentrations are associated with impaired immune regulation.

7.10. MicroRNAs:

Circulating microRNAs (miRNAs) have emerged as promising non-invasive biomarkers. Increased serum expression of **miR-21**, **miR-155**, and **miR-122** has been reported in active AIH. Because these molecules participate directly in immune regulation and hepatocyte injury, they may eventually facilitate early diagnosis, disease monitoring, and prediction of relapse (O'Connell et al., 2012).

7.11. Extracellular vesicles and exosomes:

Extracellular vesicles released by hepatocytes and immune cells contain proteins, messenger RNAs, and microRNAs reflecting the underlying inflammatory process. Although still experimental, exosome-based biomarkers may offer highly sensitive indicators of immune activity in autoimmune hepatitis.

7.12. Proteomics and Metabolomics:

High-throughput proteomic and metabolomic technologies have identified several candidate biomarkers associated with inflammatory pathways, oxidative stress, and immune activation. Integration of these approaches with genomic and transcriptomic data may support future precision medicine strategies (Mack et al., 2023).

7.13. Diagnostic Scoring Systems:

Because no individual laboratory test is diagnostic, international expert groups have developed standardized scoring systems to improve diagnostic consistency.

The **International Autoimmune Hepatitis Group (IAIHG)** originally introduced a comprehensive diagnostic scoring system incorporating clinical features, laboratory findings, autoantibodies, histopathology, viral exclusion, and treatment response (Alvarez et al., 1999). Although highly accurate, its complexity limits routine clinical application.

To facilitate everyday practice, the **Simplified IAIHG Scoring System** was introduced in 2008. This system assigns points based on four major domains:

Autoantibody positivity

Elevated serum IgG

Compatible liver histology

Exclusion of viral hepatitis

Scores of **≥6 indicate probable AIH**, while **≥7 confirm definite AIH** (Hennes et al., 2008).

These scoring systems have significantly improved diagnostic standardization worldwide and remain recommended by major hepatology societies.

Table. 3: Current Pharmacological Therapies for Autoimmune Hepatitis

Drug	Mechanism of Action	Clinical Role	Major Limitations
Prednisone/Prednisolone	Broad immunosuppression	First-line induction therapy	Long-term steroid toxicity
Azathioprine	Purine synthesis inhibition	Maintenance therapy	Bone marrow suppression, hepatotoxicity
Mycophenolate mofetil	Inhibits lymphocyte proliferation	Second-line therapy	Gastrointestinal adverse effects
Tacrolimus	Calcineurin inhibition	Refractory AIH	Nephrotoxicity, neurotoxicity
Cyclosporine	Calcineurin inhibition	Rescue therapy	Hypertension, nephrotoxicity
Rituximab	CD20 B-cell depletion	Selected refractory cases	Infection risk
Budesonide	High first-pass corticosteroid		

8. Calcineurin inhibitors:

For patients who fail to respond to corticosteroids and azathioprine or who are unable to tolerate these medications, **calcineurin inhibitors** represent important second- or third-line therapeutic options.

8.1. Tacrolimus:

Tacrolimus inhibits calcineurin phosphatase activity, thereby preventing activation of the nuclear factor of activated T cells (NFAT) signalling pathway and reducing transcription of interleukin-2 (IL-2). The consequent suppression of T-cell activation decreases cytokine production and lymphocyte proliferation. Several retrospective studies have demonstrated biochemical remission rates exceeding 60–80% in refractory AIH patients treated with tacrolimus. However, nephrotoxicity, neurotoxicity, hypertension, hyperglycaemia, and the need for therapeutic drug monitoring limit its long-term use (Than et al., 2019).

8.2. Cyclosporine:

Cyclosporine shares a similar mechanism of action by inhibiting calcineurin-mediated T-cell activation. It has shown efficacy in selected refractory cases, particularly among paediatric patients. Nevertheless, chronic nephrotoxicity, cosmetic adverse effects, hypertension, and numerous drug interactions restrict its routine application. Consequently, calcineurin inhibitors are generally reserved for specialist centres managing difficult-to-treat AIH.

9. Biological therapies:

Advances in immunology have stimulated interest in biologic agents that selectively target pathogenic immune pathways rather than producing generalized immunosuppression.

9.1. Rituximab:

Rituximab is a monoclonal antibody directed against the CD20 antigen expressed on B lymphocytes. B-cell depletion reduces autoantibody production, antigen presentation, and pro-inflammatory cytokine secretion. Small clinical studies have demonstrated encouraging responses in patients with refractory autoimmune hepatitis who failed conventional immunosuppressive therapy. Although evidence remains limited, rituximab is increasingly considered for carefully selected refractory cases (Than et al., 2019).

9.2. Anti-TNF therapy:

Tumour necrosis factor-alpha (TNF-α) is a major inflammatory mediator in AIH. Despite the theoretical rationale for TNF inhibition, clinical experience has been inconsistent. Some patients demonstrate biochemical improvement, whereas others develop paradoxical autoimmune hepatitis following anti-TNF treatment. Consequently, TNF inhibitors are **not routinely recommended** outside highly selected circumstances.

9.3. Targeting IL-17 and IL-6:

Given the central role of Th17 cells in AIH, monoclonal antibodies targeting IL-17, IL-23, and IL-6 signalling pathways are under investigation. These therapies have demonstrated efficacy in several autoimmune diseases, and preclinical evidence suggests that modulation of the Th17 axis may also benefit autoimmune hepatitis. However, robust randomized clinical trials are still lacking.

10. Regulatory T-cell therapy:

One of the most promising developments in autoimmune hepatitis is the therapeutic use of **regulatory T cells (Tregs)**.

Instead of suppressing the entire immune system, Treg therapy aims to restore physiological immune tolerance. Autologous Tregs can be isolated from peripheral blood, expanded ex vivo, and reinfused into patients to suppress autoreactive immune responses. Experimental models demonstrate that adoptive Treg transfer reduces hepatic inflammation, decreases cytokine production, and limits fibrosis progression (Longhi et al., 2020).

Even more promising is the development of **antigen-specific Tregs**, which selectively recognize hepatic autoantigens while preserving protective immunity against infections and malignancy. Although still experimental, these approaches may revolutionize AIH treatment during the coming decade.

11. Future directions:

1. Despite major advances in understanding autoimmune hepatitis, several critical questions remain unanswered. The identity of the principal hepatic autoantigens responsible for initiating disease remains incompletely defined, and the precise mechanisms responsible for loss of immune tolerance are still under investigation. Improved understanding of these fundamental processes is expected to facilitate development of antigen-specific immunotherapies capable of restoring immune tolerance without generalized immunosuppression.
2. Future research priorities include:
3. Identification of highly specific non-invasive diagnostic biomarkers.
4. Development of reliable predictors of relapse following treatment withdrawal.
5. Validation of circulating microRNAs and extracellular vesicles as biomarkers.
6. Large-scale clinical trials evaluating biologic agents and targeted cytokine inhibitors.
7. Clinical translation of regulatory T-cell therapy and CAR-Treg technology.
8. Integration of artificial intelligence into routine clinical decision-making.
9. Investigation of microbiome-directed therapeutic interventions.
10. Multi-omics approaches combining genomics, transcriptomics, metabolomics, and proteomics for individualized patient management.

International collaborative studies involving diverse ethnic populations will also be essential for understanding population-specific genetic susceptibility and optimizing personalized treatment strategies.

20. Conclusion:

Autoimmune hepatitis is a complex immune-mediated liver disease resulting from intricate interactions among genetic susceptibility, environmental triggers, dysregulated innate immunity, autoreactive adaptive immune responses, and impaired immune tolerance**.** Current evidence demonstrates that activation of Th1 and Th17 lymphocytes, dysfunction of regulatory T cells, cytotoxic $CD8^+$ T-cell-mediated hepatocyte injury, B-cell activation, and chronic inflammatory cytokine production collectively drive disease progression.

Although conventional immunosuppressive therapy with corticosteroids and azathioprine remains highly effective for most patients, treatment-related adverse effects, relapse, and refractory disease continue to present important clinical challenges. Advances in molecular immunology have substantially improved understanding of disease mechanisms and have identified numerous promising therapeutic targets, including regulatory T-cell therapy, immune checkpoint modulation, biologic agents, cytokine-directed treatments, and microbiome-based interventions.

The integration of genomics, single-cell technologies, artificial intelligence, and precision medicine is expected to transform future diagnosis and management of autoimmune hepatitis. Personalized therapeutic strategies based on individual immune signatures may ultimately replace empirical immunosuppression, improving long-term outcomes while reducing treatment toxicity.

Continued interdisciplinary collaboration among immunologists, hepatologists, molecular biologists, and computational scientists will be essential for translating these discoveries into clinical practice and improving the quality of life of patients affected by this challenging autoimmune liver disease.

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