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REVIEW

Cell Mediators of Autoimmune Hepatitis and Their Therapeutic Implications

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Abstract Autoimmune hepatitis is associated with interactive cell populations of the innate and adaptive immune systems, and these populations are amenable to therapeutic manipulation. The goals of this review are to describe the key cell populations implicated in autoimmune hepatitis and to identify investigational opportunities to develop cell-directed therapies for this disease. Studies cited in PubMed from 1972 to 2014 for autoimmune hepatitis, innate and adaptive immune systems, and therapeutic interventions were examined. Dendritic cells can promote immune tolerance to self-antigens, present neo-antigens that enhance the immune response, and expand the regulatory T cell population. Natural killer cells can secrete pro-inflammatory and anti-inflammatory cytokines and modulate the activity of dendritic cells and antigen-specific T lymphocytes. T helper 2 lymphocytes can inhibit the cytotoxic activities of T helper 1 lymphocytes and limit the expansion of T helper 17 lymphocytes. T helper 17 lymphocytes can promote inflammatory activity, and they can also up-regulate genes that protect against oxidative stress and hepatocyte apoptosis. Natural killer T cells can expand the regulatory T cell population; gamma delta lymphocytes can secrete interleukin-10, stimulate hepatic regeneration, and induce the apoptosis of hepatic stellate cells; and antigen-specific regulatory T cells can dampen immune cell proliferation and function. Pharmacological agents, neutralizing antibodies, and especially the adoptive transfer of antigen-specific regulatory T cells that have been freshly generated ex vivo are evolving as management strategies. The cells within the innate and adaptive immune systems are key contributors to the occurrence of autoimmune hepatitis, and they are attractive therapeutic targets.

Keywords Autoimmune · Innate immunity · Adaptive immunity · Interventions

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Introduction

Autoimmune hepatitis is a chronic inflammatory liver disease characterized by increased serum aminotransferase levels, autoantibodies, elevated serum immunoglobulin G (IgG) concentration, lymphoplasmocytic infiltration of the portal tract, and interface hepatitis [1]. Apoptosis is the principal mechanism of hepatocyte loss, and it can extend the inflammatory and immune responses by generating apoptotic bodies that act as neo-antigens [2]. The inflammatory response to tissue injury is a complex sequence of humoral and cellular immune reactions that reflect involvement of the innate and adaptive immune systems. The humoral response involves the sensitization of $CD4^+$ lymphocytes to self-antigens or foreign antigens that resemble self-antigens and their differentiation into antibody-producing plasma cells [3]. The cellular response involves the generation of liver-infiltrating cytotoxic $CD8^+$ lymphocytes that are the principal perpetrators of the liver injury [3]. Stress signals released from damaged hepatocytes and chemokines that attract cells of the innate immune system initiate the process [4, 5].

The principal approach to the management of autoimmune hepatitis has been to disrupt the activated pathogenic

pathways by medications with broad immunosuppressive actions [1]. Clarification and characterization of the principal cellular effectors of the disease will enhance opportunities to target these populations and alter their actions. Tools by which to manipulate the effector cell populations have emerged, and the possibility of disrupting cytokine pathways, blocking T cell antigen receptors (TCRs), strengthening favorable functions, and expanding the number and function of counter-regulatory, protective cell populations projects a new therapeutic horizon.

The goals of this review are to characterize the key components of the innate and adaptive immune systems that have been implicated in the pathogenesis of autoimmune hepatitis and to suggest investigational opportunities to develop cell-directed therapies for this disease.

Cellular Mediators in Autoimmune Hepatitis

The principal cells of the innate immune response in autoimmune liver disease are the dendritic cells and the natural killer (NK) cells [6]. The adaptive immune response emerges within the stressed microenvironment, and its highly specialized cells are able to target cells expressing "non-self" antigens and develop an immunological memory manifested as the production of autoantibodies or the development of antigen-specific TCRs. The principal components of this response are the T helper type 1 (Th1), Th2, and Th17 lymphocytes [7–9]. Natural killer T (NKT) cells, gamma delta (γδ) T cells, and regulatory T lymphocytes are also participants in the adaptive immune response [3].

Key Cellular Components of the Innate Immune System

The innate immune system constitutes the first line of defense against pathogens, and its cellular components include NK cells, mast cells, eosinophils, basophils, macrophages, neutrophils, and dendritic cells. Each cell population exhibits properties associated with both the innate and adaptive immune systems, and strict categorization by the nature of their immune response is an over simplification.

Dendritic Cells

Dendritic cells are highly specialized for uptake, processing, and presentation of foreign and self-antigens [10], and they participate in the development of immune tolerance (Table 1) [11]. Dendritic cells can respond to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) that are detected by pattern recognition receptors (PRRs) [12]. The principal PRRs on the dendritic cells are Toll-like receptors (TLRs), and they signal cell distress. Dendritic cells can recognize cell distress and migrate to areas of tissue injury (innate response), and they can present antigens to naïve lymphocytes and initiate immunological reactivity (adaptive response) [6].

The conventional dendritic cells are migratory or resident-based in lymphoid tissue, and they capture, identify, and present foreign antigens to naïve T lymphocytes (Table 1) [6]. Their major functions occur during the steady state in the absence of inflammatory signals, and they promote antigenic tolerance [6, 13]. The plasmacytoid dendritic cells respond to inflammatory signals and secrete mainly type 1 interferons (IFNs), which induce antiviral responses and promote adaptive immunity [14–17]. Plasmacytoid dendritic cells promote a Th2 immune response, and they can support the generation and function of regulatory T cells [18]. Monocyte-derived dendritic cells express high levels of the class II molecules of the major histocompatibility complex (MHC), process foreign antigens, migrate to draining lymph nodes, and sensitize naïve T lymphocytes to specific antigens (Table 1) [6].

Studies in experimental animal and human models of diverse immune-mediated diseases, including systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, autoimmune thyroid disease, and multiple sclerosis (experimental autoimmune encephalomyelitis), have supported the role of dendritic cells in the induction of autoimmunity [6, 15, 19]. Autoimmune liver disease has been produced in animal models by the vaccination of C57BL/6 mice with dendritic cells loaded with well-differentiated hepatocellular carcinoma cells [20], and fatal autoimmune hepatitis has been induced in a mouse model from dendritic cells that induced the differentiation of naïve T lymphocytes to Th1 cells and cytotoxic T cells in response to interleukin (IL)-18 [21].

Natural Killer Cells

Natural killer (NK) cells comprise up to 15 % of the peripheral blood lymphocytes and 30–50 % of the resident hepatic lymphocytes (Table 1) [22–24]. Their number and availability attest to their importance as components of the innate immune response and protectors against invading pathogens [24]. NK cells also interact with antigen-producing cells (dendritic cells and T lymphocytes), and they can exhibit features associated with an adaptive immune response [25]. The severity of diverse tissue-specific, immune-mediated diseases, including autoimmune hepatitis [26], primary biliary cirrhosis (PBC) [27], systemic sclerosis [28], rheumatoid arthritis [29], and type 1 diabetes mellitus [30], are influenced by the activity of NK cells.

Table 1 Principal cell populations of the innate immune response in tissue-specific autoimmunity

Cell population	Functions
Dendritic cells (DC)	Quiescent state:
	Capture, identification, and processing of foreign antigens [6]
	Cross-presentation of antigens on class I MHC molecules [6]
	Promotion of regulatory T cell population [19]
	Induction of antigen-specific tolerance [6]
	Inflammatory state:
	Respond to PAMPs and DAMPs [6, 12]
	Possess PRRs (mainly TLRs) [6, 12]
	Phagocytize apoptotic bodies [6]
	Autoantigen-presentation and lymphocyte sensitization [6]
	Initiation of adaptive immune response [6]
Monocyte-derived DCs	Derived from bone marrow as monocytes [6]
	Differentiation into dendritic cells during inflammation [6]
	Expression of class II MHC molecules [6]
	Sensitization of naive T lymphocytes to specific antigens [6]
Conventional DCs	Migratory or resident based in lymphoid tissue [6]
	Capture and presentation of foreign antigens to naive T lymphocytes [6]
	Promotion of antigenic tolerance in quiescent state [6]
	Promotion of adaptive immune response in inflammatory state [6]
Plasmacytoid DCs	Activation by inflammatory signals [6, 15]
	Production of type 1 interferons [17]
	Promotion of Th2 immune response [15, 17, 18]
	Induction of regulatory T cells [18]
Myeloid DCs	Inclusion of monocyte-derived DCs and conventional DCs [6]
	Secretion of IL-12 and IL-23 [6]
	Promotion of Th1 and Th17 immune responses [6]
NK cells	Cross-talk with dendritic cells and T lymphocytes [22, 24, 33]
	Lysis of distressed cells lacking surface class I MHC molecules [24, 33]
	Limitation of fibrosis by lysing hepatic stellate cells [22]
	Production of pro-inflammatory and anti-inflammatory (IL-10) cytokines [22]

Numbers in brackets are references

DAMP damage-associated molecular pattern, *DCs* dendritic cells, *IL* interleukin, *MHC* major histocompatibility complex, *NK* natural killer, *PAMP* pathogen-associated molecular pattern, *PRR* pattern recognition receptors, *Th* T helper, *TLR* Toll-like receptors

NK cells have two principal sets of receptors that modulate their activity in humans, and they are the killer immunoglobulin (Ig)-like receptors (KIRs) and the C2D natural killer group 2 member D (NKG2D) receptors (Table 1) [24]. NK cells with stimulatory KIRs can lyse distressed cells that cannot be identified as self [31], and NK cells with inhibitory KIRs can suppress cytolytic activity [32]. Self is defined mainly by the ability to express class I MHC molecules on the cell surface, and NK cells with stimulatory KIRs do not target cells expressing these molecules [33]. Combinations of KIRs can define haplotypes that reflect an inherited balance between inhibitory and stimulatory receptors, and occurrences of systemic sclerosis, type 1 diabetes mellitus, and rheumatoid vasculitis have been associated with certain KIR genotypes [33].

NKG2D receptors are expressed on all NK cells, and they direct NK cells to ligands expressed on distressed cells [34]. The soluble forms of the MHC class I-related chains A and B (MIC A and MIC B) are membrane glycoproteins that are induced by cell stress, and these glycoproteins can activate NK cells by ligating with their NKG2D receptors and inducing cytolysis [35]. Serum levels of MIC A and MIC B have been low or absent in patients with autoimmune hepatitis, PBC, and PSC [36], and the role of the NGK2D ligands in the pathogenesis of these autoimmune liver diseases is unclear. The observation that a strong activator of hepatic NK cells (polyinosinic:polycytidylic acid) can produce an NK cell-dependent hepatitis that mimics autoimmune hepatitis advances the candidacy of this population as a critical participant in the occurrence of this disease [37].

Key Cellular Components of the Adaptive Immune System

The adaptive immune system consists of T and B lymphocytes that have been differentiated into highly

Table 2 Principal cell populations of the adaptive immune response in tissue-specific autoimmunity

Cell population	Functions
Th1 lymphocytes	Generation of antigen-specific cytotoxic $CD8^+$ T lymphocytes [8]
	Secretion of pro-inflammatory cytokines (IL-2, TNF-α, and IFN-γ) [8, 40]
	Inhibition of Th17 cells [7]
Th2 lymphocytes	Generation of antibody-dependent cell-mediated cytotoxicity [8, 43]
	Secretion of anti-inflammatory cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-25) [8]
	Inhibition of Th1 cells, Th17 cells, monocytes, and macrophages [43]
Th17 lymphocytes	Secretion of pro-inflammatory cytokines (IL-17A, IFN-γ) [7, 9]
	First responders of adaptive immune system [45]
	Association with tissue injury and disease severity [45]
	Suppression of regulatory T cell function [48]
	Secretion of anti-inflammatory cytokine IL-22 [44]
NKT cells	Secretion of pro-inflammatory cytokines(IFN-γ, IL-4, IL-21) [50, 51, 55]
	Apoptosis of distressed cells [54]
	Recognition of CD1d molecules by purinergic P2X7 receptors [57]
	Immune inhibition or stimulation as directed by glycolipids [52]
	Activation of B cells, T cells, NK cells, and other NKT cells [54]
	Expansion of regulatory T cells [56]
	Activation of hepatic stellate cells and promotion of hepatic fibrosis [51]
Gamma delta (γδ) T cells	Recognition of damage patterns and prompt migration to sites of injury [59]
	Phagocytosis of invading pathogens [61]
	Antigen recognition linked to class Ib MHC molecules [62]
	Apoptosis of distressed cells [59]
	Secretion of pro-(IFN-γ, IL-17) and anti-(IL-10) inflammatory cytokines [59]
	Down-regulation of NKT cells and $CD8^+$ T cells [63]
	Induction of hepatic stellate cell apoptosis [59]
Regulatory T lymphocytes	Inhibition of IFN-γ production and hepatic stellate cell proliferation [41, 77]
	Secretion of anti-inflammatory cytokine IL-10 [78]
	Suppression of IL-17 production and proliferation of Th17 cells [79, 80]
	Conversion of ATP and ADP to AMP and AMP to adenosine [86, 88]
	Apoptosis of Th1 and dendritic cells by galectin-9 and TIM-3 ligation [90]

Numbers in brackets are references

ADP adenosine diphosphate, *AMP* adenosine monophosphate, *ATP* adenosine triphosphate, *CD* cluster of differentiation, *IFN* interferon, *IL* interleukin, *MHC* major histocompatibility complex, *NK* natural killer, *NKT* natural killer T, *Th* T helper, *TIM-3* T cell immunoglobulin and mucin domain-3 receptor, *TNF-α* tumor necrosis factor-alpha

specialized subsets that can recognize, neutralize, and remember specific antigens [38]. The effector cell populations that can clonally expand and produce antibodies or infiltrate tissue (Th1, Th2, and Th17 lymphocytes) and the cell populations that can modulate the immune response (NKT cells, γδ cells, and regulatory T cells) are the key subsets implicated in tissue-specific autoimmune diseases and relevant to autoimmune hepatitis [38].

Th1 Lymphocytes

Th1 lymphocytes are sensitized to foreign antigens that have been presented in the antigen-binding groove of class II MHC molecules by APCs (Table 2) [39]. The activated Th1 lymphocytes then differentiate along a type 1 cytokine pathway, mediated mainly by IL-2, interferon-gamma (INF-γ), and tumor necrosis factor-alpha (TNF-α), into tissue-infiltrating cytotoxic $CD8^+$ lymphocytes. The cytotoxic $CD8^+$ lymphocytes target and destroy distressed cells, mainly by inducing their apoptosis [3]. The apoptotic bodies may subsequently be phagocytized and presented as neo-antigens by APCs (dendritic cells) [2]. In autoimmune hepatitis, the foreign antigens may resemble self-antigens (molecular mimicry), and repeated or intense exposures to these antigens may override self-tolerance and induce autoreactivity [3].

Th17 cells secrete the pro-inflammatory cytokines, IL-6, IL-1, and TNF-α, and they recruit Th1 cells to sites of tissue damage. The Th1 lymphocytes can in turn produce IFN-γ, and this cytokine can inhibit the further expansion of the Th17 cells in a counter-regulatory loop [7]. The pro-inflammatory cytokines, IL-2, IFN-γ, and TNF-α, secreted by the Th1 lymphocytes strengthen the adaptive immune response by boosting the expression of class I MHC molecules on APCs, increasing the expression of class II MHC molecules on hepatocytes, and promoting the proliferation

of cytotoxic $CD8^+$ lymphocytes [40]. Current management strategies for autoimmune hepatitis are directed at inhibiting the activation, differentiation, and proliferation of the Th1 lymphocytes by pharmacological agents [1].

Th2 Lymphocytes

Th2 lymphocytes are sensitized by foreign antigens presented by the class II MHC molecules expressed on APCs. In contrast to Th1 lymphocytes, these cells differentiate into B lymphocytes that can expand into clones of plasma cells (Table 2) [3]. The plasma cells in turn can produce immunoglobulin, generate antibodies, and support an antibody-dependent cell-mediated cytotoxicity [3]. Th2 lymphocytes are induced by IL-4 [8]. They also secrete IL-4, and they can expand in an autocrine fashion.

Th2 lymphocytes secrete IL-5, IL-9, IL-10, IL-13, and IL-25 in addition to IL-4 [8], and they express messenger RNA for peroxisome proliferator-activated receptor-gamma (PPAR-γ), which is a nuclear receptor that can inhibit the expression of pro-inflammatory genes [41]. IL-4 inhibits the proliferation of Th17 lymphocytes [7]; IL-5 induces the expansion of antigen-specific regulatory T cells [42]; and IL-10 dampens the inflammatory response [8, 41]. The composite effect of cytokine production by the Th2 lymphocytes is to reduce inflammation by inhibiting Th1 cells, Th17 cells, monocytes, and macrophages and by expanding the regulatory T cell population [43].

Th17 Lymphocytes

T helper 17 (Th17) lymphocytes are a subset of $CD4^+$ lymphocytes that are generated from naïve lymphocytes by the cytokines, IL-6, and TGF-β (Table 2) [9, 44]. Th17 cells may constitute the first wave of effector cells within the liver in response to inflammatory injury. Their number is increased in the peripheral blood and liver tissue of patients with autoimmune hepatitis, and they have been associated with the severity of inflammatory activity and advanced fibrosis [45]. Th17 cells may also have a protective effect on the liver. Th17 cells secrete IL-22, and IL-22 may have anti-inflammatory effects that counterbalance the pro-inflammatory actions of IL-17 [46, 47]. In a murine model of acute alcoholic hepatitis, treatment with recombinant IL-22 reduced hepatic steatosis and up-regulated genes with anti-oxidant and anti-apoptotic effects [47].

Th17 cells have a positive feedback loop that sustains the inflammatory and immune-mediated responses within the liver (Table 2) [8, 44]. The production of IL-17 by the Th17 cells can induce the hepatic production of IL-6 [45]. Increased production of IL-6 can in turn promote the proliferation of Th17 cells by synergizing with TGF-β [45, 48]. These interactions can also intensify inflammatory activity by reciprocally suppressing regulatory T cell function [48]. The dual cytotoxic and protective actions of the Th17 cells and the dependence of these actions on the cytokine milieu afford opportunities for molecular manipulations that may have therapeutic relevance in immune-mediated diseases such as autoimmune hepatitis.

Natural Killer T Cells

NKT cells reside within the liver, and they have surface markers and functions similar to T lymphocytes and NK cells (Table 2) [49]. NKT cells respond rapidly to hepatic injury (innate immune response), and they can modulate the innate and adaptive immune responses by secreting pro-inflammatory and anti-inflammatory cytokines [50]. NKT cells can also behave as specialized, antigen-reactive T lymphocytes (adaptive immune response) [51]. The NKT cells that rapidly respond to sites of tissue damage have a semi-invariant T cell antigen receptor chain, and they have been classified as invariant NKT (iNKT) cells [49, 51]. The predominant action of the iNKT cells (stimulatory or inhibitory) is modulated in part by the nature of the sensitizing glycolipid antigens released at the sight of tissue injury [52]. iNKT cells recognize CD1d molecules [53], which are a family of class I MHC molecules that present endogenous and exogenous lipid antigens to CD1-restricted cells [52, 54].

The rapid migration of NKT cells to the injured site can extend the liver injury or promote a reparative response (Table 2) [51]. NKT cells are constitutively cytotoxic in that they can induce the apoptosis of distressed cells by releasing granzymes and perforin [54], and they can promote the inflammatory response by producing IFN-γ, IL-4, and IL-21 [55]. These stimulatory actions can in turn be modulated by the ability of NKT cells to promote the differentiation of regulatory T cells [56]. Animal models that are deficient in NKT cells do not develop experimental immune-mediated liver disease [57], and the NKT cells may influence the occurrence and severity of autoimmune hepatitis [58].

Gamma Delta T Lymphocytes

Gamma delta (γδ) T cells constitute 15–25 % of the T lymphocytes within the liver [59], and they are characterized by a TCR composed of one gamma (γ) chain and one delta (δ) chain (Table 2) [59]. The composition of the TCR distinguishes this population from the majority of T lymphocytes whose TCRs consist of one alpha (α) and one beta (β) chain. Gamma delta T cells can exhibit a range of functions that include innate and adaptive immune responses [60]. TCRs can recognize DAMPs and respond rapidly to cellular distress signals and non-peptide ligands

without antigen priming [60], and they can phagocytize invading pathogens [61]. Subsets may also develop antigen recognition, specificity, and memory that are linked to the class Ib MHC molecules [62]. They can kill target cells by receptor-mediated apoptosis or the release of cytolytic granules [59], and they may protect against immune-mediated tissue damage and collagen deposition by down-regulating $CD8^+$ cytotoxic T cells [63] and inducing the apoptosis of hepatic stellate cells [64].

Gamma delta T cells have been described in the peripheral blood and liver of patients with autoimmune liver disease, but the contribution of these cells to the disease process is unclear (Table 2). The percentage and absolute numbers of γδ T cells have been higher in the peripheral blood of children with autoimmune hepatitis or PSC compared to healthy subjects [65], and the accumulation of γδ T cells has been greater in the portal tracts of liver tissue from patients with autoimmune hepatitis, PBC, or PSC than from control specimens [66]. The increased hepatic accumulation of γδ T cells has lacked specificity for autoimmune liver disease, but it has supported speculation that the γδ T cells are effectors of liver damage [67]. Countering these pathogenic attributes have been protective actions that can reduce the inflammatory response by IL-10 production [68], impair hepatic fibrosis by inducing Fas-mediated apoptosis of hepatic stellate cells [64], and promote hepatic regeneration by secreting IL-17 and IL-22 [69]. The phenotypic and functional plasticity of γδ T cells strengthens their candidacy as important contributors to the pathogenesis of autoimmune liver disease and therapeutic targets in autoimmune hepatitis.

Regulatory T Cells

Regulatory T cells are a small but critical subset of $CD4^+$ T lymphocytes that are characterized by a constellation of distinctive surface markers and by immunosuppressive actions that dampen the immune response (Table 2) [4, 70]. Two main subtypes of the regulatory T cells have been described, and they are the natural regulatory T cells and the induced regulatory T cells [71]. Natural regulatory T cells develop in the thymus, and they constitute 10 % of the $CD4^+$ lymphocytes in the peripheral blood [72]. The induced regulatory T cells develop in an inflammatory milieu after antigen exposure and stimulation by TGF-β [73]. The peripherally induced regulatory T cells exert more powerful immunosuppressive effects than the natural, thymic-derived, regulatory T cells [74]. Furthermore, the induced regulatory T cells maintain phenotypic and functional stability in inflammatory conditions, whereas natural regulatory T cells can lose suppressive function when exposed to pro-inflammatory cytokines. Natural regulatory T cells can convert to Th1, Th2, and Th17 effector cells [75].

The principal function of the regulatory T cells is to suppress immune-mediated responses. Regulatory T cells expressing PPAR-γ inhibit the production of IFN-γ by $CD4^+$ lymphocytes [41], suppress the inflammatory response in murine models [76], and inhibit the proliferation and chemotaxis of hepatic stellate cells [77]. Regulatory T cells also strengthen the type 2 anti-inflammatory cytokine pathway by producing IL-10 [78], and they limit the proliferation of Th17 cells by suppressing the production of IL-17 [79, 80]. Neonatal thymectomy in a mouse model depletes $CD4^+$-$CD25^+$ regulatory T cells, accelerates antibody responses, and increases the frequency of pathogenic self-reactive T cells [81, 82]. In BALB/c mice with disruption of the programmed cell death-1 ($PD\text{-}1^{-/-}$) signaling pathway, neonatal thymectomy is associated with loss of natural $Foxp3^+$ regulatory T cells and the spontaneous development of fatal autoimmune hepatitis [83–85]. These findings underscore the importance of natural, thymic-derived, regulatory T cells in maintaining immunological homeostasis and preventing an unregulated autoreactive response.

Two molecular signaling pathways influence the function of the regulatory T cells. CD39 is an ectonucleotidase that is expressed on regulatory T cells, and it catalyzes the conversion of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to adenosine monophosphate (AMP) [86]. AMP in turn is converted to the immune regulatory nucleoside, adenosine, by CD73 which is derived mainly from contiguous damaged tissue [87]. Adenosine in turn suppresses the proliferation and cytokine secretion of Th1 and Th2 lymphocytes [88].

The galectin-9-TIM-3 pathway is another mechanism by which the regulatory T cells can maintain immunological homeostasis. Galectin 9 is a beta galactosidase-binding protein expressed on regulatory T cells, and it promotes immune tolerance by binding to the T cell immunoglobulin and mucin domain-3 receptor (TIM-3) which is expressed on Th1 cells and dendritic cells [89, 90]. The ligation of galectin 9 with TIM-3 induces the apoptosis of Th1 and dendritic cells and down-regulates the immune response [90]. Deficiencies in the expression of galectin 9 on regulatory T cells and TIM-3 on the Th1 cells have been associated with autoimmune hepatitis, and correction of these deficiencies is another treatment opportunity in autoimmune hepatitis [89].

Key Chemokine Pathways Affecting Effector Cell Migration

The diverse cellular components of the innate and adaptive immune systems are directed to sites of liver injury mainly by the release of chemokines from the injured hepatic tissue [4, 5]. Chemokines function as ligands (L) that attract immune and inflammatory cells with complementary ligand

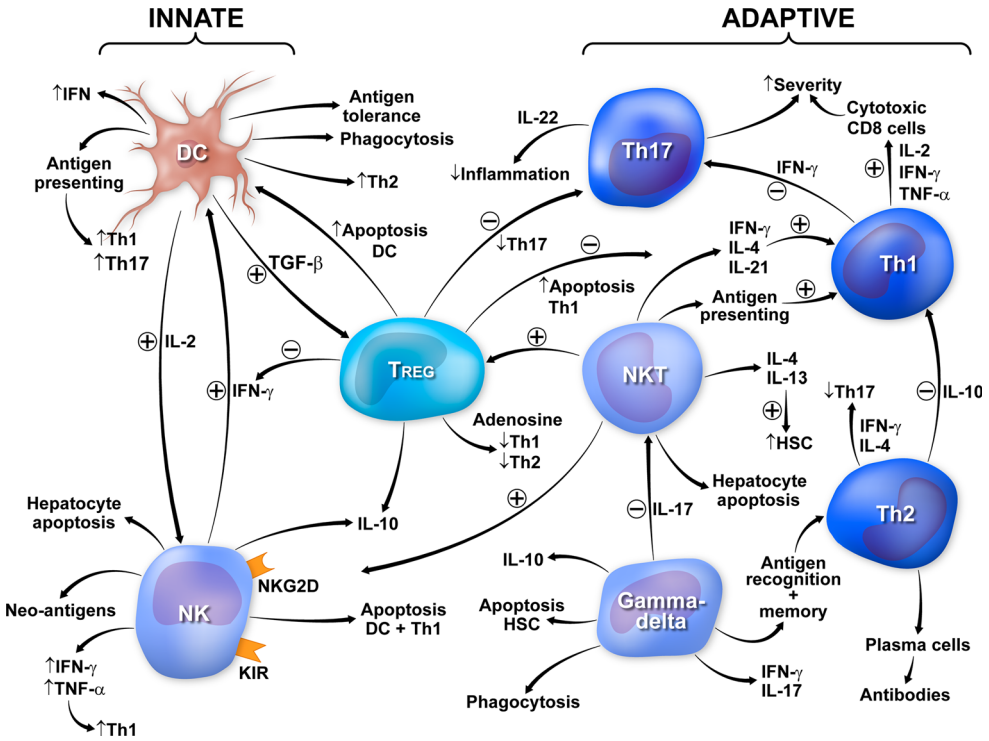

Fig. 1 Interactive inhibitory and stimulatory actions of the innate and adaptive immune systems in autoimmune hepatitis. Dendritic cells (DC) and natural killer (NK) cells are the principal components of the innate immune response, and they secrete interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin (IL)-2. These cytokines have pro-inflammatory actions on the T helper type 1 (Th1) and T helper type 17 (Th17) lymphocytes. NK cells are characterized by the expression of killer immunoglobulin-like receptors (KIR) and C2D natural killer group 2 member D (NKG2D) receptors. Th1, Th type 2 (Th2), and Th17 lymphocytes; natural killer T (NKT) cells; and gamma delta lymphocytes are the principal components of the adaptive immune response. Each cell population has inhibitory (−) and stimulatory (+) actions mediated by the secretion of pro-inflammatory (IFN-γ, TNF-α, IL-2, IL-4, IL-17, IL-21) and anti-inflammatory (IL-22, IL-10) cytokines depending on the cell type. The cells of the adaptive immune response can modulate the severity of tissue injury by stimulating expansion of regulatory T cells (Treg) and inducing the apoptosis of hepatocytes and hepatic stellate cells (HSC)

receptors (R) [91]. The chemokines can be produced by injured resident cells within the liver (hepatocytes, endothelial cells, hepatic stellate cells, and dendritic cells) and by first responder cells (neutrophils and monocytes) [92]. The cellular responders can in turn generate a positive feedback loop by producing cytokines, stimulating chemokine production, and attracting effector cells [93]. The effects of the chemokines and their ligands can vary during the course of the disease, and different liver diseases may have different cytokine profiles [5, 94]. Chemokines typically promote pro-inflammatory and pro-fibrotic responses, but they can also have anti-inflammatory and anti-fibrotic actions [5].

The principal chemokine ligands implicated in immune-mediated liver diseases are CXCL9, CXCL10, CXCL11, CCL20, CXCL12 (stromal cell-derived factor-1 [SDF-1]) and CX3CL1 [fractalkine]) [4]. Serum levels of eotaxin-1 (CCL11), eotaxin-3 (CCL26), and CCL11 (macrophage-derived chemokine [MDC]) are increased in autoimmune hepatitis, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) [94]. CX3CL1 (fractalkine), which is expressed by hepatocytes, hepatic stellate cells, and biliary endothelial cells, has pro-inflammatory and anti-fibrotic effects [95, 96]. Its cognate receptor, CX3CR1, is expressed on monocytes, Kupffer cells, natural killer cells, T lymphocytes, and smooth muscle cells [97, 98]. The CX3CR1/CX3CL1 axis may protect hepatocytes from apoptosis [97, 99], limit the accumulation of monocyte-derived macrophages in the liver [97], inhibit Kupffer cell production of TGF-β [98], impair the activation of hepatic stellate cells [98], and reduce the deposition of collagen [90]. The net effects of the cell mediators in autoimmune hepatitis are influenced by the chemokine milieu associated with the hepatic injury, and therapeutic manipulations of this milieu by pharmacological agents or neutralizing antibodies are possible management strategies [4, 5].

Feasible Cell-Based Interventions in Autoimmune Hepatitis

The principal cell populations that have been implicated in the pathogenesis of autoimmune hepatitis have complex,

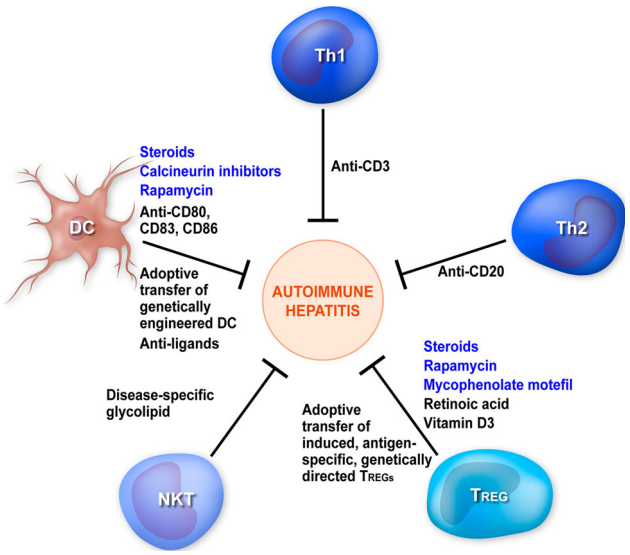

Fig. 2 Current and prospective cell-directed interventions in autoimmune hepatitis. Pharmacological therapies (*blue*) are current treatments for autoimmune hepatitis, and they have non-selective effects on dendritic cells (DC) and regulatory T cells (Tregs). Investigational interventions (*black*) include antibodies to cell surface markers (anti-CD3, CD20, CD80, CD83 and CD86), adoptive transfer of key cell populations, moderation of activity with engineered antigens (glycolipids), and agents that strengthen immunosuppressive actions (retinoic acid, vitamin D3). The investigational therapies have been directed mainly against the T helper type 1 (Th1) lymphocytes, Th2 lymphocytes, Tregs, natural killer T (NKT) cells, and DC

frequently opposite actions that can stimulate or inhibit the immune responses (Fig. 1). Each population and their molecular signals are feasible therapeutic targets. Intrinsic, possibly inherited, defects in cell function may be irreparable, and the restoration of immunological homeostasis may depend mainly on strengthening the salutary actions of a single population or on generating a composite beneficial effect from several populations. The challenge of immune cell manipulation is to preserve or strengthen the protective actions while restricting or isolating the deleterious effects. The ideal candidates for therapeutic manipulation in autoimmune hepatitis are well-characterized, antigen-activated, cell populations that have a broad impact on the disease and that can be accurately targeted. Regulatory T cells, cytotoxic Th1 lymphocytes, antibody-producing Th2 lymphocytes, NKT cells, and dendritic cells have these attributes.

Therapy Directed at Regulatory T Cells

Autoimmune hepatitis has been associated with quantitative and qualitative deficiencies in the regulatory T cell population [100], albeit these observations have been challenged [101]. CD39-positive regulatory T cells are decreased in number, hydrolyze ATP and ADP to AMP less actively, and fail to suppress IL-17 production by $CD4^+$ lymphocytes [80]. They also have less lineage stability compared to the regulatory T cells of healthy subjects after an inflammatory challenge. The increased production of the pro-inflammatory cytokines, IFN-γ and IL-17, by the CD39-positive regulatory T cells suggests that these cells have undergone a phenotypic conversion from an immunosuppressive to a pro-inflammatory state [80]. These deficiencies and transformations within the regulatory T cell population are key aspects of autoimmune hepatitis that can be targeted by pharmacological [102, 103] and cellular interventions (Fig. 2) [104, 105].

Pharmacological Agents

Corticosteroids can reconstitute the regulatory T cell population, and the regulatory T cells can in turn suppress the proliferation of $CD8^+$ lymphocytes and induce the production of the anti-inflammatory cytokine, IL-4 (Table 3) [102]. Mycophenolate mofetil can expand the regulatory T cell population [106–108], possibly by directly inhibiting the expression of co-stimulatory molecules (CD40, CD80, CD86) by dendritic cells, impairing the presentation of antigens, and reducing the production of the pro-inflammatory cytokine, IL-12 [6, 109]. Rapamycin can also increase the population of functional antigen-specific regulatory T cells, [103, 110] and in murine models treated with various immunosuppressive agents, rapamycin has been superior to mycophenolate mofetil as an expander of this population [110].

Other less conventional agents have had similar success in restoring the function of regulatory T cells (Table 3). Retinoic acid has been able to abrogate inflammation-induced deficits in regulatory T cell function and limit the increase of Th1 and Th17 transcription factors during inflammatory activity [103]. The activated form of vitamin D3 (1, 25 dihydroxyvitamin D3) can induce the immunosuppressive actions of the regulatory T cells and promote tolerance to allografts of pancreatic tissue in murine models of transplantation (Fig. 2) [106]. Vitamin D3 inhibits antigen-presentation by dendritic cells, limits the production of IL-12, increases the secretion of IL-10, and supports the immunosuppressive actions of invariant NKT cells [106, 111].

Low serum levels of 25-hydroxyvitamin D have been found in 43 % of patients with autoimmune hepatitis, and low 25-hydroxyvitamin D levels have been associated with advanced hepatic fibrosis and severe inflammation [112]. Furthermore, polymorphisms of the vitamin D receptor gene have been described with autoimmune hepatitis [113, 114], and low serum levels of 25-hydroxyvitamin D have been identified in diverse, non-liver-related, immune-mediated diseases, including multiple sclerosis, rheumatoid

Table 3 Feasible cell-directed therapeutic considerations in autoimmune hepatitis

Target population	Treatment consideration	Putative effects
Regulatory T cells	Corticosteroids	Restoration of normal number and function [102]
	Mycophenolate mofetil	Inhibition of co-stimulatory molecules by DC [6]
		Expansion of regulatory T cell population [106]
		Reduction of IL-12 production [109]
	Rapamycin	Expansion of functional, antigen-specific population [110]
	1, 25 dihydroxyvitamin D3	Inhibition of antigen presentation by DC [106]
		Reduction of IL-12 production and stimulation of IL-10 [106]
	Retinoic acid	Restoration of function [103]
	Adoptive transfer	Restoration of function and immune tolerance [105, 116]
Th1 lymphocytes	Non-mitogenic anti-CD3	Induction of effector cell apoptosis by targeting TCR [126]
		Strengthen regulatory T cell function by TGF-β [126, 127]
Th2 lymphocytes	Antibodies to CD20	Induction of B cell apoptosis and clonal depletion [130]
		Enhancement of regulatory T cell population [130]
NKT cells	Glycolipid antigens	Promotion of disease-specific favorable actions [52, 136–138]
	Anti-cytokine antibodies	Inhibition of cytokines to skew T lymphocyte actions [139]
Dendritic cells	Immunosuppressive drugs	Inhibition of activation, function, cytokine production [141–143]
	Neutralizing antibodies	Prevention of intracellular stimulatory signaling [144, 145]
	TLR2 agonists	Induction of antigen tolerance [146]
	Genetic alterations	*Ex vivo* generation of genetically engineered DC [147]
	Oligonucleotides	Blockade of stimulatory surface molecules [148]
	Vaccination	Elimination of antigen-specific clones [149]
	Metabolic disruptions	Inhibition of maturation and cytokine production [150]
	Adoptive transfer	Unaltered autologous dendritic cells (Phase I trial) [140]

Numbers in brackets are references

DC dendritic cells, *IL* interleukin, *NKT cells* natural killer T cells, *TCR* T cell antigen receptor, *TGF-β* transforming growth factor-beta, *TLR2* toll-like receptor 2

arthritis, inflammatory bowel disease, and systemic lupus erythematosus [115]. The disease-specific modulatory dysfunctions of the immune system associated with vitamin D deficiency are unclear, but disturbances in the regulatory T cell population must be considered.

Current pharmacological agents may also be rendered more effective by better understanding the mechanisms for their failure and identifying strategies for re-enforcing their actions. Studies in thymectomized neonatal mice have indicated that spontaneous fatal autoimmune hepatitis is associated with splenic follicular helper T cells which can migrate into the liver via the CCR6–CCL20 axis [84, 85]. These mice have depletion of $Foxp3^{+}$ regulatory T cells and disruption of the PD-1 signaling pathway, and they are resistant to treatment with dexamethasone. Splenectomy has prevented the development of autoimmune hepatitis in this experimental model, and it has suppressed liver inflammation and improved survival after administration of dexamethasone [85]. These findings identify the spleen as the induction site for experimental autoimmune hepatitis in animals deficient in regulatory T cells, and they suggest that failures of current drug regimens might be overcome by ancillary measures that not only replenish the regulatory T cell population but also target reservoirs of autoreactive cells.

Adoptive Transfer

Aberrations in the number and function of the regulatory T cells in autoimmune hepatitis can also be corrected by the adoptive transfer of regulatory T cells that have been expanded or newly generated [104, 105, 116], and this intervention has improved histological indices of disease activity and restored peripheral tolerance to liver antigens in a murine model of experimental autoimmune hepatitis (Table 3) [105]. Newly generated regulatory T cells proliferate more actively and resist apoptosis more fully than expanded populations [116]. By inhibiting IL-17 production in culture, freshly generated regulatory T cells can maintain a stable phenotype, lose pro-inflammatory properties, and improve their immunosuppressive actions [117].

Antigen-specific regulatory T cells also have greater immunosuppressive effects than non-antigen-specific polyclonal regulatory T cells [118, 119]. Antigen

specificity facilitates migration of the regulatory T cells to the appropriate tissue site, and it promotes their activation in the target organ without affecting their function [120]. Regulatory T cells can be engineered to have organ specificity without knowledge of the particular antigen that actually triggers the disease [120, 121]. They can be directed to the appropriate target by the retroviral transfer of the preferred TCR [122] or the incorporation of a chimeric antigen receptor (CAR) [123].

The prospect of restoring immune tolerance favors the adoptive transfer of antigen-specific regulatory T cells over pharmacological agents with indiscriminate immunosuppressive actions in the management of autoimmune hepatitis [104]. The challenge is to universalize a treatment which is highly individualized, labor-intensive, expensive, and restricted to specialized centers [104, 124].

Therapy Directed at Th1 Lymphocytes

Non-mitogenic monoclonal antibodies to CD3 dampen tissue damage by the cytotoxic $CD8^+$ cells through direct and indirect actions (Table 3) [125]. The antibodies target the TCR of mature T lymphocytes, and they induce degradation of deoxyribonucleic acid and promote cell death by apoptosis (direct action) (Fig. 2) [126]. They also augment the function of regulatory T cells by promoting the secretion of TGF-β by macrophages and immature dendritic cells (indirect action) [126, 127]. Macrophages and immature dendritic cells phagocytize the apoptotic bodies of the dying cytotoxic T lymphocytes, and they release TGF-β which in turn induces the activity of regulatory T cells and enhances immunosuppression. Treatment has been effective in animal models of diabetes [128] and experimental autoimmune encephalitis [126] and in patients with autoimmune diabetes [129].

Therapy Directed at Th2 Lymphocytes

Rituximab is a chimeric mouse–human monoclonal antibody that binds to CD20 on the B cell surface, induces apoptosis, and achieves rapid and sustained depletion of B cells [130]. Isolated case reports have indicated the success of rituximab in the treatment of autoimmune hepatitis and idiopathic thrombocytopenic purpura [131], autoimmune hepatitis and cryoglobulinemic glomerulonephritis [132], autoimmune hepatitis and previous B cell lymphoma [133], and autoimmune hepatitis and Evans syndrome (autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura) (Table 3) [134]. Furthermore, a single-center experience involving six patients with refractory autoimmune hepatitis has demonstrated significant reductions in serum aspartate aminotransferase levels at 24 weeks, histological improvement in the 4 patients who underwent liver tissue examination, and no serious side effects after two infusions of rituximab (1,000 mg) 2 weeks apart (Fig. 2) [135].

Therapy Directed at NKT Cells

Injections of the marine sponge-derived glycosphingolipid, α-galactosylceramide, into a murine model of systemic lupus erythematosus can confer long-term protection by activating NKT cells that inhibit the proliferation of IL-10 producing B cells (Table 3) [136]. Treatments with α-galactosylceramide [137] or a synthetic analog of this same glycolipid [138] have protected mice from autoimmune diabetes and from collagen-induced arthritis (Fig. 2). Modifications in the length and structure of the acyl chain on the synthetic α-galactosylceramide molecule can alter the NKT cell response, and this molecular plasticity suggests that the structure of the glycolipid antigen can be designed to suit the disease and the individual patient [137]. Actions of the NKT cells can also be modified by blocking the production of certain cytokines and dampening their effect on the maturation and proliferation of effector T cell populations [125]. Neutralizing antibodies against pro-inflammatory (IL-21) and anti-inflammatory (IL-4, IL-10) cytokines can skew the function of T lymphocytes along a favorable pathway (Table 3) [139].

Therapy Directed at Dendritic Cells

The challenge in developing therapies directed at dendritic cells is to neutralize the target early in the disease without critically disrupting immunological homeostasis or allowing epitope spread [6]. Treatments that have been evaluated in animal models include pharmacological agents, neutralizing antibodies, tolerance induction, gene therapy, vaccination, adoptive transfer, and metabolic disruption [6, 140]. The multitude of options reflects the preliminary nature of the investigations and the lack of a clear preference (Fig. 2).

Corticosteroids impair dendritic cell function, and they are the principal medications used in the treatment of autoimmune hepatitis (Table 3) [141]. The calcineurin inhibitors down-regulate dendritic cell production of the pro-inflammatory cytokines, IL-2 and IL-12, and they inhibit the activation of memory $CD8^+$ T lymphocytes and the differentiation of antigen-sensitized T lymphocytes [142]. Rapamycin impairs the activation of dendritic cells, prevents their maturation, and preserves tolerance to self-antigens [143]. These medications are currently used in the management of autoimmune hepatitis, and they have non-selective actions and variable results.

Molecular interventions may improve the precision of cell targeting, neutralize a critical pathogenic pathway, and achieve a durable result (Table 3) [6]. Antibodies to the surface markers of dendritic cells (CD80, CD83, and CD86) can prevent their maturation by inhibiting co-stimulatory interactions with CD28 receptors on autoreactive T lymphocytes [144], and antibodies to the delta-like ligand 4 (anti-Dll4) can block a signaling (Notch) pathway important in the development of dendritic cells [145]. The chronic stimulation of the Toll-like receptor 2 (TLR2) has prevented diabetes in a murine model by enhancing the induction of antigen tolerance by dendritic cells [146], and dendritic cells that have been generated ex vivo from harvested monocytes, transfected with genes encoding IL-10, and adoptively transferred to mice have reduced graft rejection [147]. Additional efforts of some success have included the down-regulation of dendritic cells ex vivo by oligonucleotides targeting the surface molecules, CD40, CD80, and CD86, prior to their injection into syngeneic diabetic mice [148], and the administration of unaltered autologous dendritic cells by adoptive transfer to patients with type 1 diabetes (Phase I clinical trial) [139].

Other interventions in early stages of evaluation are dendritic cell vaccines based on the linkage of a dominant autoantigen with an immune stimulatory adjuvant to inhibit dendritic cell maturation [149] and the administration of enzymes (indoleamine 2, 3 diogenase) or metabolites (3-hydroxyanthranilic acid) that inhibit the maturation of dendritic cells, their production of pro-inflammatory cytokines (IL-6, IL-12 and TNF-α), and their activation of Th1 lymphocytes (Table 3) [150].

Overview

Cells of the innate and adaptive immune systems are the principal effectors of tissue-specific immune-mediated diseases, and this highly interactive and cross-regulatory network of cell populations is amenable to therapeutic manipulation (Fig. 1). The interventions that have progressed furthest in the treatment of autoimmune hepatitis have focused on the regulatory T cell population. The adoptive transfer of regulatory T cells, especially antigen-specific cells that have been freshly generated and highly purified, has emerged as an intervention that may induce a durable, antigen-specific, immune tolerance, and it has improved the histological features of experimental autoimmune hepatitis in mice (Fig. 2) [105].

Cell-directed interventions affecting the number and actions of the Th1 and Th2 lymphocytes, NKT cells, and dendritic cells are ongoing in other immune-mediated diseases, and they may also have relevance in autoimmune hepatitis (Fig. 2). Non-mitogenic monoclonal antibodies to CD3 can target the cytotoxic $CD8^+$ T cells that are the principal effectors of autoimmune hepatitis [129], and antibodies to CD20 have already shown promise in this disease [135]. Each intervention is poised for formal study. The contributions of the NKT cells and dendritic cells to the occurrence and severity of autoimmune hepatitis are uncertain, but their key roles in the genesis of other tissue-specific autoimmune diseases and the emergence of methods to alter them justify a continuing interest in these populations as future therapeutic targets [6, 137].

The goals of inducing a durable tolerance of pathogenic antigens and restoring immune homeostasis by correcting or counteracting deficiencies or excesses in the cellular perpetrators of the disease constitute a natural progression in the management of immune-mediated disorders. The advances that are occurring in the understanding and management of these diseases must continue to excite and energize investigational efforts in autoimmune hepatitis.

Conflict of interest None.

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