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The bidirectional immune crosstalk in metabolic dysfunction-associated steatotic liver disease (MASLD)

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is an unabated risk factor for end-stage liver diseases with no available therapies. Dysregulated immune responses are critical culprits of MASLD pathogenesis. Independent contributions from either the innate or adaptive arms of the immune system or their unidirectional interplay are commonly studied in MASLD. However, the bidirectional communication between innate and adaptive immune systems, and its impact on MASLD, remains insufficiently understood. Given that both innate and adaptive immune cells are indispensable for the development and progression of inflammation in MASLD,

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elucidating pathogenic contributions stemming from the bidirectional interplay between these two arms holds potential for development of novel therapeutics for MASLD. Here, we review the immune cell types and bidirectional pathways that influence the pathogenesis of MASLD, and highlight potential pharmacologic approaches to combat MASLD based on current knowledge of this bidirectional crosstalk.

eTOC blurb

To date, immunological studies of MASLD have focused on discrete immune regulators and unidirectional mechanisms. Here, Sawada et al. review the bidirectional immune pathways that influence the pathogenesis of MASLD and highlight potential pharmacologic approaches based on this crosstalk.

Keywords

immune crosstalk; adaptive immunity; innate immunity; MASLD; MASH; NAFLD; NASH

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) refers to a spectrum of liver disorders ranging from metabolic dysfunction-associated steatotic liver (MASL) to metabolic dysfunction-associated steatohepatitis (MASH)[1,2]. MASL is characterized by triglyceride deposition in hepatocytes with no or very minor inflammation and no hepatocyte ballooning, which is typically considered a reversible state. To be classified under the MASLD umbrella, steatosis is associated with at least one cardiometabolic risk factor such as obesity[3], dyslipidemia, hypertension, and insulin resistance without excessive alcohol intake[2]. MASH, on the other hand, involves lobular inflammation, fibrosis, and hepatocyte ballooning, which can progress to irreversible fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)[4,5].

The use of MASLD, MASL, and MASH was recently endorsed by pan-national liver associations (American Association for Study of Liver Disease [AASLD], European Association for Study of the Liver [EASL], and Asociación Latinoamericana para el Estudio del Hígado [ALEH]) via a Delphi process in replacement of non-alcoholic fatty liver disease (NAFLD), non-alcoholic fatty liver (NAFL), and non-alcoholic steatohepatitis (NASH), respectively, to reduce stigma and enhance disease awareness, understanding, and drug/biomarker development with the new nomenclature and diagnostic criteria[2]. Notably, because this change in nomenclature occurred during development of this review, all literature cited utilize NAFLD terminology and diagnostic criteria. However, a retrospective study found that 98% of individuals that fulfilled the criteria for NAFLD also fulfilled those for MASLD[6], providing reasonable rationale to consider findings from older NAFLD studies as valid under the new MASLD definition. Thus, to avoid confusion we will use the new MASLD nomenclature when referencing cited literature.

Epidemiological studies, using NAFLD diagnostic classifications, found that 20–30% of adults with MASL develop MASH[7], with 20–50% of individuals with MASH approximated

to progress to cirrhosis[8]. Even in those that don't progress to cirrhosis, about 13–49% of all HCCs develop in individuals with noncirrhotic MASH[9]. In pediatric populations diagnosed with MASLD via biopsy, 25–50% have MASH and 10–25% have advanced fibrosis at initial presentation[10–14]. MASH poses a significant risk for advanced liver diseases (the fastest growing cause of HCC[15]) and liver failure (the largest cause of liver transplant in women and the second largest in men[16], and the fastest growing indication of the need for liver transplantation[15,17]), in addition to vascular (e.g., portal hypertension[18], cardiovascular disease [CVD][19]) and metabolic (e.g., type 2 diabetes [T2DM][20]) complications. Although MASLD represents a significant clinical burden, approved pharmacological therapies to prevent or treat MASLD are not available[21] despite the numerous potential avenues currently being explored[22]. Thus, vast efforts are underway to elucidate the mechanisms by which MASL progresses to MASH.

Dogmatically, the multi-hit hypothesis is believed to shape MASLD development and progression[23,24]. The initial hit, hepatocyte triglyceride accumulation, sensitizes and predisposes hepatocytes to subsequent hits that drive and regulate disease progression and pathogenicity. Lipotoxicity[25], reactive oxygen species (ROS) production[26,27], intestinal microbiome[28], and induction of proinflammatory immune mediators are all proposed as mechanisms associated with MASLD pathogenesis. Because these "second hits" are not specific to the liver, MASLD is considered not only a hepatic but also a systemic inflammatory disease[29,30]. Moreover, it is recognized that non-liver tissues also significantly contribute to the pathogenesis of MASLD. Although critical in MASLD pathogenesis, mediators of systemic inflammation[31], as well as contributions of adipose[32,33] and muscle[34,35] tissue inflammation to MASLD have been reviewed elsewhere[31]. Thus, here we focus specifically on immune responses that shape liver tissue inflammation in MASLD.

Different types of mouse models have been employed for the study of MASLD, notably those involving various dietary challenges including altered caloric content (e.g., high fat diet [HFD][36], MASH diet[37]) or deficient in specific nutrients (e.g., methionine-choline deficient [MCD] diet[38], choline-deficient, L-amino acid defined [CDAA] diet[39]), and chemical perturbations (e.g., carbon tetrachloride [CCl_4][40]). Due to the wide scope of MASLD, each animal model recapitulates certain aspects of MASLD and not the entire disease spectra. For example, HFD feeding drives robust steatosis with minimal MASH/fibrosis[41,42], while MCD diet induces hepatic inflammation, hepatocellular damage, and cirrhosis without obesity[43]. Of note, HFD feeding in combination with thermoneutral housing was recently shown to have a potential to unlock modeling of full MASLD spectra in mice[43] and to uncover novel processes that instruct immune responses in MASLD progression.

The immune responses need to be tightly regulated in type, timing, and amplitude. Delayed or insufficient vigor of immune response can result in inadequate protection from bacterial, fungal, and viral infections. Conversely, too vigorous of a response can itself be harmful – which is seen, paradigmatically, in the development of inflammatory diseases (e.g., rheumatoid arthritis, type I diabetes, psoriasis, atopic dermatitis and systemic lupus erythematosus) (reviewed in [44]). Further, the pathophysiology of these autoimmune diseases is linked to dysregulated proinflammatory cytokine (e.g., TNF, IL-6, IFNγ, IL-1β,

IL-23, type I IFNs) production (reviewed in [45]). Homeostatic production of these immune mediators is involved in the physiology of healthy liver, while an aberrant production is associated with both obesity and MASLD pathogenesis (e.g., hepatic inflammation, fibrosis and hepatocellular damage) (reviewed in [46]). Thus, it is not surprising that research endeavors in the field have focused on identifying the key immune and non-immune cells that produce these proinflammatory immune mediators, the processes that control their production, and the mechanisms by which these mediators drive MASLD pathogenesis.

The immune mediators produced by resident liver parenchymal cells as well as resident and infiltrating immune cells can additively activate both innate and adaptive immune systems that in turn drive MASLD development and progression. Notably, studies conducted on immune responses in MASLD have traditionally focused on the role of innate immunity in disease development and progression. Recent reports, however, have highlighted the sufficiency of innate immunity to cause MASL while the adaptive arm is required for development and progression of MASH[47] (Figure 1A). Hence, recent research directions have in part shifted towards improved understanding of the role of adaptive immunity in MASLD pathogenesis. Despite such efforts, the MASLD research has largely adopted a linear progression of inflammation, where innate immune responses unidirectionally instruct the function of adaptive immune responses (Figure 1B). However, such views largely omit the key novel discoveries in the field of immunology: the communication between innate and adaptive immune systems is in fact a bidirectional process[48–50] – whereby the cells of the adaptive immune system also activate and instruct the function of innate immune responses[51–53]. Thus, understanding the contributions of the bidirectional communication may be important for unlocking the enigma of immune responses and immune cell function in MASLD that may aid in the development of novel therapeutics (Figure 1C). Here, based on this new knowledge, we review the innate and adaptive immune cells involved in the bidirectional crosstalk, the cellular/molecular mechanisms underlying this bidirectional immune communication, and speculate on the potential immune therapeutic approaches for MASLD via manipulation of the bidirectional crosstalk.

Immunological landscape in MASLD pathogenesis

Despite substantial research to understand the immune cell function in MASLD, additional in-depth investigations of cellular subsets and mechanisms relevant to MASLD pathogenesis are needed. A comprehensive review of the varied immune cell populations and their impact on the inflammatory progression of MASLD has been recently covered extensively elsewhere[54]. Thus, here we only provide an introductory overview of key innate and adaptive immune cells to MASLD that are critically involved in pathways of bidirectional communication introduced in the “Innate and Adaptive Immune Cell Crosstalk” section that follows (Figure 2).

Innate immunity

Liver is enriched with various subsets of innate immune cells, including the liver-resident macrophage subsets, and immune cell populations including neutrophils, dendritic cells (DCs), natural killer (NK) cells, and natural killer T (NKT) cells. Activation of these cells

and subsequent dysregulated production of inflammatory cytokines amplify hepatic accrual of immune cells and exacerbate inflammation and hepatocellular damage[55,56].

Macrophages: Two major subsets of macrophages are present in the liver – liver resident macrophages or Kupffer cells (KCs), and monocyte-derived macrophages (Mo-Ms) recruited from circulation. Various mechanisms by which KCs and Mo-Ms contribute to MASLD, MASH and HCC progression are reviewed in detail in multiple recent literature[57–59]. In obesity, pathogen-associated molecular patterns (PAMPs; e.g., LPS, bacterial DNAs) are increased which directly activates KCs[60,61]. Specifically, in MASH, Toll-like receptor (TLR) 4 expression in KCs is higher compared to other TLRs[62]. Notably, LPS binding to TLR4 triggers MAPK, p38, NF-κB signaling[63,64] to induce proinflammatory cytokine (e.g., TNF, IL-1β, IL-12) and chemokine (e.g., CCL2, CCL5) secretion that promotes local inflammation. Mo-Ms are recruited to the liver by injured hepatocytes or activated KCs[65], adding on to the diversity of hepatic macrophage populations in MASLD[66]. Thus, in the MASLD/MASH mouse livers, the composition of the hepatic macrophage pool is altered, as recruited Mo-Ms and KCs derived from recruited monocytes replace embryonic KCs[67–70]. Mo-Ms exhibit proinflammatory phenotypes that augment liver injury and drive disease progression[65], as mice lacking Mo-Ms (e.g., *Ccr2*$^{-/-}$ mice) show less CDAA diet-driven steatosis, hepatic inflammatory cell infiltration, and fibrosis[71].

Neutrophils: Neutrophils are one of the first leukocytes recruited to the liver following KC activation via PAMPs[72,73]. Neutrophil hepatic accrual instigates a proinflammatory environment by robust secretion of IL-6, which promotes tissue inflammation and fibrosis[74,75]. By recruiting additional Mo-Ms and interacting with other antigen presenting cells (APCs), neutrophils amplify the feed forward inflammatory cascade[76]. Additionally, the release of neutrophil granule proteins (e.g., myeloperoxidase, neutrophil elastase, proteinase 3) promotes ROS production and NETosis[77–79], which cumulatively enhances inflammation, hepatocellular damage, and progression to HCC[80]. Notably, neutrophil-to-lymphocyte ratio is positively correlated with MASLD severity, and indicative of higher risk of advanced cirrhosis[81] and HCC[82] among individuals with MASLD, suggesting the key role neutrophils play in MASLD progression.

Dendritic cells (DC): Hepatic DCs are heterogeneous population that can be grouped into plasmacytoid DCs (PDCA-1^{+}; pDCs) and myeloid/classical DCs (PDCA-1^{-}; mDCs), with further sub-groups[83]. Depending on the cellular subtypes and environmental cues, DCs can promote both proinflammatory[84] and antiinflammatory[85] responses. In healthy livers, DCs predominantly display an immature phenotype exemplified by a low capacity to endocytose antigens and stimulate T lymphocytes[86]. However, during hepatic injury or with increased cellular lipid content, DCs switch to an immunogenic phenotype with enhanced capacity to present antigens and increased proinflammatory cytokine production[87]. Of note, a recent study identified LKB1-AMPK/SIK signaling axis as a mechanism by which DCs limit Th17 polarization in the liver and play a protective role in MASLD[88]. Thus, given that the heterogeneity and divergent functional effects of hepatic DCs in MASLD are disease stage-dependent, their definitive role in MASLD pathogenesis is yet to be defined[89,90].

Natural Killer (NK) cells: Hepatic NK cells represent a heterogeneous population, which is further amplified during disease state[91–93] and is likely responsible for the divergent findings in their role in MASLD (reviewed in [94]). In individuals with MASH, increased circulating/conventional NK (cNK) cells are found in the liver[95] along with elevated expressions of the activating receptor NKG2D and its ligands MIC A/B in the liver parenchyma[96]. Together, these processes suggest that activation of NK cells occurs in MASLD. Notably, NK cells convert toward ILC1-like phenotype and become less cytotoxic in obese livers of both humans and mice[97]. Such changes in NK cell population during MASLD may lead to differential outcomes of either promoting or preventing disease progression. These variable effects in disease progression may also depend on disease stage, as NK cell proinflammatory function is postulated to drive MASH but also hinder HCC[98,99].

Natural Killer T (NKT) cells: Depending on the mechanisms of activation, the type 1 or invariant natural killer T (iNKT) cells have both proinflammatory and antiinflammatory effector functions, accompanied by rapid production of cytokines in large amounts[100]. HFD-fed mice lacking iNKT cells show higher susceptibility to weight gain and steatosis[101], along with increased hepatic inflammation, ALT levels, and fibrosis[102], supporting protective/antiinflammatory roles of iNKT cells in MASLD. Mechanistically, iNKT cells contribute to obesity-driven hepatic immune balance by CD206-mediated crosstalk with an antiinflammatory, IL-10 producing KC subset (KC-1)[103]. In early stages of MASLD, iNKT cells are recruited to the liver and secrete IL-4, promoting the resolution of hepatic inflammation and aiding in liver injury repair[104]. Protective roles of iNKT cells were also suggested upon disease progression to HCC, via their antiinflammatory properties during oncogenic β-catenin-induced liver inflammation[105]. Notably, obesity-associated hepatic cholesterol accumulation was found to selectively suppress NKT cell antitumor surveillance in the liver[106]. On the other hand, pathogenic involvement of NKT cells in MASLD was also reported; accumulation of NKT cells is associated with exacerbated fibrosis in MASH[107], and LIGHT secreted by NKT cells was shown to activate NF-κB signaling that facilitates steatosis and MASH to HCC transition[47]. These contradictory data may be attributable to their varying effector functions[108,109], in addition to the variations in immunological landscape dependent on the disease stage[110].

Other innate immune cell types: In addition to those introduced above, innate lymphoid cells (ILCs) and mucosal associated invariant T (MAIT) cells have been suggested to contribute to MASH pathogenesis. Despite having overlapping effector functions with $CD4^+$ T cells in obesity[111–115], the literature on ILCs and MAIT cells in MASLD is somewhat limited. Specifically, reduced ILC1[116] and increased ILC3[117] numbers are reported in MASLD, while increase in ILC2 is seen in fibrotic liver[118] and in the liver of individuals with HCC[119]. Meanwhile, hepatic MAIT cell numbers are increased in MASLD[120] and in individuals with MASLD-related cirrhosis[121], where they are believed to exhibit profibrogenic properties[121]. In contrast, mice with genetic ablation of MR1 (MHC class I-related protein; expression restricted to MAIT cells[122]) fed MCD diet develop severe steatosis and proinflammatory characteristics[120].

Adaptive immunity

Adaptive immunity includes cell-mediated and humoral immunity, mediated principally by T and B lymphocytes, respectively. The major T lymphocytes involved in adaptive immunity include $CD4^+$ T cells (further categorized into T helper [Th] 1, Th2, Th17, regulatory T [T_{reg}] cells, etc.), $CD8^+$ T cells, and γδ T cells[123]. B lymphocytes are similarly classified into different subsets including transitional, naïve, memory, double negative, regulatory, B1, and antibody secreting B cells[124]. Growing attention is being directed towards the role of adaptive immunity in MASLD, leading to ongoing discoveries about its involvement in MASH[7].

$CD4^+$ T cells: $CD4^+$ T cells are highly plastic immune cells, capable of shaping both pro- and antiinflammatory landscape. $CD4^+$ T cells are grouped according to their cytokine production and transcription factor expression, including Th1 (IFNγ; Tbet), Th2 (IL-4; GATA3), Th17 (IL-17; RORγt), and T_{reg} (IL-10/TGFβ; FOXP3)[125,126] cells. Despite the divergent reports on the shift in the number of total hepatic $CD4^+$ T cells in MASLD (e.g., progressive hepatic accrual in MASLD[127,128] or decreased hepatic presence in transition to HCC[129]), published reports suggest that polarization of $CD4^+$ T cells towards Th1[130] and Th17[128,131] subsets along with increased production of IFNγ and IL-17A[132–136] contributes to MASLD progression[129,137,138]. Blocking integrin-mediated hepatic recruitment of $CD4^+$ T cells attenuated hepatic inflammation and fibrosis in mouse model of MASLD, providing further evidence of the necessity of $CD4^+$ T cells in MASLD pathogenesis[139].

Th1 and Th2 cells are implicated in MASH pathogenesis by skewed balance of elevated proinflammatory Th1 responses relative to reduced antiinflammatory Th2 responses[137]. Accumulation of Th1 cells and increased systemic and hepatic IFNγ are reported in individuals with MASH[140]. In fact, IFNγ is considered a pathogenic contributor to MASLD progression, as genetic ablation of IFNγ in mice protects from MASH and hepatic fibrosis[141]. In contrast, the role of Th2 cells in MASLD is poorly understood. Although increased number of Th2 cells in the peripheral blood of individuals with MASLD are reported[95], the implications of such alterations remain unclear. The antiinflammatory cytokines produced by Th2 cells may alleviate hepatic inflammation, while their high profibrogenic potential[142] may contribute to progression towards cirrhosis.

Th17 cells, via amplification of proinflammatory signals that sustain tissue inflammation, are considered major contributors to MASLD pathogenesis, with IL-17A believed to be a key cytokine driving this process[76,135,143,144]. In MASLD, hepatic Th17 cell numbers are increased in mice[36] and hepatic presence of IL-17A producing cells is associated with steatosis to MASH transition in humans[131]. Mechanistically, IL-17 induces the expression of chemokines (e.g., CXCL1, CCL2) that facilitate neutrophil and macrophage infiltration and activation and amplify tissue inflammation and fibrogenesis[143,145]. Recently, a subset of highly inflammatory hepatic Th17 cells that express CXCR3 and co-produce IL-17A, IFNγ, and TNF was identified as a critical contributor to MASLD pathogenesis[128]. The number of these inflammatory hepatic Th17 cells increases during MASLD progression in mice, and their presence correlates with MASLD severity in humans[128].

T_{reg} cells, via regulation of effector T cell activation, serve as critical immune regulators that prevent the excessive activation of pathogenic immune responses. However, the role of T_{reg} cells in MASH progression remains incompletely defined. The frequency of hepatic T_{reg} cells decreases in experimental models of HFD-driven MASLD[129,146] and is associated with increased oxidative stress in liver microenvironment[147]. In addition, adoptive transfer of splenic T_{reg} cells from lean mice into obese animals attenuated hepatocellular damage and inflammation, suggesting that T_{reg} cells restrict MASLD progression[147]. However, in MASH models using choline-deficient diet with HFD feeding and diethylnitrosamine injections[148] or high fat high carbohydrate diet[149], increase in hepatic T_{reg} cells was observed. Further, T_{reg} cell depletion ameliorated the progression to HCC[148] and adoptive transfer of T_{reg} cells to animals with MASH exacerbated steatosis and liver damage[149] in these models. Human studies on T_{reg} cells in MASLD are similarly conflicting, with both increased[138,150] and reduced[131] frequency and numbers of intrahepatic T_{reg} cells being reported.

CD8$^+$ T cells: The contributions of CD8$^+$ T cells to MASLD pathogenesis are context dependent. CD8$^+$ T cell numbers are increased in the liver of individuals with MASH[47], and inhibition of CD8$^+$ T cell function in animal model decreases hepatic steatosis and inflammation[151]. Hepatic accrual of activated CD8$^+$ T cells[152] amplifies the proinflammatory environment via increased production of IFNγ and TNF and induces cytotoxic activity-driven hepatocellular damage[153]. Upon reversal of disease progression, however, CD8$^+$ T cells directly contribute to the resolution of hepatic inflammation and fibrosis[154]. Of note, MASH reduces CD8$^+$ T cell mobility by inducing metabolic/mitochondrial dysfunction[152] and impairs tumor antigen-specific CD8$^+$ T cell response[155], ultimately leading to HCC progression.

B cells: Although limited, existing evidence supports a pathogenic role for B cells in MASLD[156]. Hepatic B cell accrual is seen in both humans[157] and mice[158] with MASLD and is accompanied by higher B cell expression of inflammatory mediators (e.g., IL-6, TNF). Whether B cell production of these mediators directly promotes MASLD pathogenesis, or indirectly amplifies hepatic inflammation via induction of CD4$^+$ T cell differentiation towards Th1/Th17 cells in MASLD liver remains unknown[158]. In some individuals with MASLD, elevated levels of circulating IgA, IgM, and IgG were reported[159]. Specifically, circulating IgG levels against oxidative stress-derived epitopes (anti-OSE IgG) are increased in MASLD[157,160,161]. Of note, loss of IL-10 producing regulatory B cells in mice with MASLD has been reported[162].

Innate and Adaptive Immune Cell Crosstalk

The bidirectional crosstalk between adaptive and innate immune cells has recently been linked with critical immune cell inflammatory functions[163]. Given the increased recognition on the roles of peripheral and intrahepatic adaptive immune cells in MASLD[109,156], understanding the bidirectional crosstalk between innate and adaptive immune cells in MASLD pathogenesis is of high priority. In this section, we review receptor/ligand interactions known to play a role in the bidirectional crosstalk between innate and adaptive immune cells and discuss their potential roles in MASLD (summarized in Table 1).

Receptor/ligand-driven communication pathways between innate and adaptive immune cells

Signal transduction through co-stimulatory molecules represents a key method of communication between the cells of the innate and adaptive immune systems. Although both antigen dependent and independent activation of the adaptive immune cells have been suggested to play a role in MASLD pathogenesis[164,165], much of the research to date has focused on the processes dependent on antigen encounter and innate immune cell activation. For example, upon activation of the T cell receptor (TCR) signaling pathway, upregulated co-stimulatory molecules colocalize with TCR and subsequently engage with their respective ligands/receptors expressed on APCs and pathogen-experienced hematopoietic/non-hematopoietic cells to further promote immune cell activation and function[166–169]. While the implications of signal transduction downstream of the co-stimulatory receptor in T cells are relatively well understood, the capabilities of the ligands and their interaction with co-stimulatory receptors to “reverse signal” to the APCs to enhance their activation and/or function remain underappreciated[170–173] (Figure 3A,B). Critically, recent reports demonstrate the direct ability of effector T cells to instruct innate immune cell functions[52,53]. Hence, here we discuss the key pathways of bidirectional communication between innate and adaptive immune cells and how they contribute to MASLD.

CD28/B7.1 & B7.2 Signaling: The function of CD28 expressed on T cells is best characterized in the context of T cell activation[174]. Though less appreciated, CD28 also promotes long lived plasma cell survival[175], neutrophil chemokine and chemokine receptor expression[176,177], NKT cell development[178], and eosinophil cytokine production[179]. The interactions of B7.1 (CD80) and B7.2 (CD86) expressed on APCs[180] with CD28 expressed on T cells induces DC-centric secretion of inflammatory mediators[173], in turn initiating inflammatory responses in both T cells and APCs. Mice with genetic ablation of CD28 have lower hepatic triglyceride accumulation, inflammation, and hepatocellular damage in HFD driven MASLD[181]. The CD28 deficient mice also express lower hepatic levels of *Foxp3*, invoking the role of CD28 in maintaining hepatic T_{reg} cell pool. Because T_{reg} cells are canonically considered antiinflammatory, CD28 may indirectly counter MASLD progression via its effects on hepatic T_{reg} cell accrual. Correspondingly, mice with genetic deletion of B7.1 and B7.2 exhibit augmented MASLD pathology and reduced T_{reg} cell numbers when fed HFD[182]. These findings suggest that CD28/B7 interaction and signaling is critical for maintaining T_{reg} cell population and could play a beneficial role in MASLD. However, blockade of B7 signaling via anti-B7.1/B7.2 antibodies ameliorates hepatic steatosis and inflammation without skewing T_{reg} cell development and numbers[182]. Hence, these data support a pathogenic involvement of CD28/B7 signaling when its effects on T_{reg} cells are masked. Combined, the existing data imply a divergent role of CD28/B7 signaling dependent on its effects on T_{reg} cells. Unlike in mice, the role of CD28/B7 signaling has not been directly studied in human MASLD. A case study report demonstrated a dramatic improvement in insulin resistance in an individual treated with abatacept (CTLA-4 Ig, a fusion protein of cytotoxic T lymphocyte antigen 4 [CTLA-4] linked to IgG designed to inhibit CD28-B7 binding)[183]. Whether and how CD28 signaling, and more specifically

the immune crosstalk mediated by this pathway, shapes MASLD pathogenesis in humans remains to be investigated.

4–1 BB/4–1BBL Signaling: Initially identified as a specific co-stimulatory receptor expressed on activated T cells[184], it is now appreciated that 4–1BB (CD137) is also expressed on B cells, NKT cells, DCs, neutrophils, and macrophages where it similarly promotes their effector functions[168,185,186]. 4–1BBL (CD137L), the ligand for 4–1BB, propagates the reverse signaling that promotes proinflammatory functions of B cells, DCs, and macrophages/monocytes[187,188], while also limiting T cell effector functions[189]. In mice fed HFD, hepatic expression of 4–1BB and 4–1BBL is elevated compared to chow fed counterparts[190]. Further, 4–1BB-deficient mice exhibit attenuated HFD-driven hepatic steatosis and inflammation[190]. Analysis of 4–1BB expression in human HCC tumor microenvironment revealed that 4–1BB is almost exclusively expressed on tumor-infiltrating $CD8^+$ T cells[191]. Because the individuals recruited for this study were not limited to those with underlying metabolic dysfunction, whether the 4–1BB upregulation is specific to HCC precipitated from MASLD remains to be elucidated.

OX40/OX40L Signaling: OX40 (CD134), a co-stimulatory receptor induced in activated T cells[192], also impacts the function and survival of NKT cells, NK cells, and neutrophils[167]. The reverse signaling through its ligand OX40L (CD252) promotes DC proinflammatory function[188], B cell proliferation and antibody production[193], and T cell survival[194]. Notably, individuals with MASH have higher plasma levels of soluble OX40 compared with healthy controls, and OX40 levels positively correlate with MASH severity[195]. In experimental models of MASLD, OX40 and OX40L expression within hepatic mononuclear cells and the plasma levels of soluble OX40 are increased[195]. In addition, OX40-deficiency in T cells is linked with lower hepatic immune cell (e.g., monocytes, Th1 and Th17 cells) accrual and proinflammatory function, and lower MASH severity[195].

CD40/CD40L Signaling: CD40 receptor is expressed specifically on APCs and enhances APC proinflammatory phenotype and function[169]. CD40L (CD154), the ligand for CD40, is expressed on activated T cells and enhances T cell effector functions while also inducing T cell apoptosis[196–198]. The involvement of CD40 signaling in MASLD pathogenesis is reviewed in detail elsewhere[199]. HFD fed CD40 deficient mice (both whole body and $CD11c^+$ DC-specific knockout models[200–202]), despite amplified hepatic steatosis, do not exhibit hepatic inflammation. However, in MASH, despite similar hepatic steatosis, liver inflammation is reduced in mice lacking CD40 in $CD11c^+$ cells compared to wild type controls[200]. The differential effects of the two diets were attributed to divergent hepatic T_{reg} cell accrual. On the other hand, the data regarding the role of CD40L in MASLD pathogenesis is less consistent. CD40L-deficient mice exhibit varying severity of hepatic steatosis in experimental models of MASLD[203–205], depending on the diet and genetic background of animals used. Given the divergent findings and the ability of CD40L to bind to two other receptors in addition to CD40[206], the need for further in-depth ligand/receptor studies is highlighted.

Fas/FasL Signaling: Canonically considered an inducer of apoptotic cell death of Fas (CD95)-expressing cells[207], Fas signaling also contributes to the activation of both innate and adaptive immune responses. Specifically, FasL (CD178) is required for adequate $CD8^+$ T cell proliferation upon TCR engagement[208], in addition to contributing to T cell thymic development[209], invoking a role of FasL as a costimulatory signal. Induction of Fas signaling in innate immune cells, by FasL expressed on $CD4^+$ T cells, leads to pathogen-independent IL-1β production[52]. Further, Fas signaling at-large leads to macrophage polarization[210], neutrophil migration[211], and germinal center B cell homeostasis[212]. In individuals with MASH, levels of soluble Fas and FasL in serum as well as hepatic Fas expression are elevated compared to healthy individuals[213,214]. Similarly, mice with hepatocyte-specific ablation of Fas have reduced HFD-driven hepatic steatosis[215].

Cytokine-driven communication pathways between innate and adaptive immune cells

In addition to the communication pathways through receptor/ligand interactions introduced above, communication between innate immune cells and adaptive immune cells, especially B cells, can also occur in the form of soluble factors[216] (Figure 3C,D). Here we discuss the contributions of select mediators including type I interferons (IFN-I), B cell activation factor (BAFF)/a proliferation-inducing ligand (APRIL), and IL-6 in MASLD pathogenesis.

Type I Interferon (IFN-I) Signaling: While almost all cells can produce and respond to IFN-I[217–221], IFN-I produced by pDCs upregulate TLR7 expression, and sensitivity of TLR7-induced maturation, in naïve B cells[216,222]. Conversely, B cells produce IFN-I in response to TLR9 ligation[223], and pDCs depend on IFN-I for their activation and migration[224]. Both TLR7 and TLR9 activation is viewed as a critical driver of MASLD[225,226], with TLR9 signaling in intrahepatic B cells proposed to dominantly drive its inflammatory gene expression[227]. Further, highlighted by the necessity of IFN-1 receptor (IFNAR) expression to induce HFD-driven steatosis in mice[228], IFN-I play a key role in MASLD development[228–233] (reviewed extensively in [234]), and pDC-driven IFN-I promotes induction of obesity[235].

B cell activation factor (BAFF)/A proliferation-inducing ligand (APRIL) Signaling: B cell survival and maturation in the periphery, including the liver, is dependent on signals induced by BAFF (CD257) and its close homolog APRIL (CD256)[236–238]. Both BAFF and APRIL are predominately expressed by innate immune cells in response to proinflammatory cytokines and TLR signaling activation[239–241]. Their cognate receptors are transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI or CD267), B-cell maturation antigen (BCMA or CD269), and BAFF receptor (BAFF-R or CD268)[241–243]. Both BAFF and APRIL bind to TACI and BCMA, while BAFF also binds to BAFF-R[238]. Activation of these receptors induces transcription of genes that shape inflammatory functions of B cells[244–247], $CD4^+$ T cells[248], DCs[249], and monocytes[250], while it can also shape adipocyte function[251]. Although reverse signaling through BAFF/APRIL is understudied, signaling via membrane-bound BAFF and APRIL in macrophages induces expression of proinflammatory mediators[187,252,253]. Of note, BAFF serum levels are reduced in individuals with obesity and are negatively correlated with body mass index (BMI)[251], which suggests that BAFF may contribute to aspects of MASLD pathogenesis

that is divergent from those linked to metabolic derangements. In mouse models of MASLD, those deficient of BAFF display reduced hepatic steatosis[157,254], while those with overexpressed BAFF are protected from hepatocellular damage[251]. In congruence with these results, APRIL deficient mice, with increased serum BAFF levels, exhibit reduced hepatocellular damage[251]. Whether the impact of BAFF/APRIL on MASLD pathogenesis is dependent on the expressing cell type or the receptor(s) they act through is unknown. To this end, inhibition of TACI signaling selectively depletes marginal zone and B2 B cells[255], and in experimental mouse models of MASLD, TACI signaling inhibition reduces hepatic inflammation and fibrosis[157,251,256].

Interleukin 6 (IL-6) Signaling: IL-6, a pleotropic proinflammatory cytokine, is produced by both immune and non-immune cells[257]. Although first discovered for its stimulatory effects on B cells[258], it is now appreciated that IL-6 regulates inflammatory functions of $CD4^+$ T cells[259], DCs[260], macrophages[261], neutrophils[262], and NK cells[263,264]. In humans, increased circulating and hepatic IL-6 levels are reported in MASLD[265]. In mice, increased hepatic B cell accrual as well as increased production of IL-6 by hepatic B cells is reported in MASLD[158]. Interestingly, inhibition of IL-6 signaling via MR16–1 (an IL-6 receptor neutralizing antibody) in mice fed MCD diet enhanced hepatic steatosis but alleviated hepatocellular damage[266]. Whether IL-6 production by, and IL-6 receptor signaling in immune cells is sufficient/required for MASLD pathogenesis is yet to be elucidated.

Immune cell crosstalk modulation in MASLD: towards therapy

While considerable progress in elucidating the role of immune responses in pathogenesis of MASLD has been made, no specific immune therapies to MASLD exist. Although immune cell depletion therapies might restrict MASH progression, unwanted side effects that involve immunosuppression and toxicity warrant development of more selective therapies for MASLD. Thus, more discriminatory strategies that target specific immune cell recruitment and/or costimulatory pathways, including potential inhibition of the activation of both arms of the immune system through the bidirectional crosstalk, could represent a viable avenue for MASLD treatment.

Targeting cytokine signaling has proved useful in the treatment of various inflammatory diseases. For example, inhibitors of IL-17 and IL-23 signaling are FDA approved or have shown promising results in late-stage clinical trials for treatment of inflammatory diseases that share immunopathological features with MASLD/MASH[267–275]. To this end, clinical studies targeting cytokine-driven pathways of immune crosstalk, especially IFN-I, IL-6, and TNF, have shown strong potential for inflammatory disease treatment (Table 2). IFN-α kinoid (immunotherapeutic vaccine that induces the generation of IFN-neutralizing antibodies[276]) treatment lowered disease activity state in individuals with systemic lupus erythematosus (SLE) with further assessment in a phase III clinical trial announced[276]. Similarly, anifrolumab (IFN-α/β receptor blocking antibody) treatment improved clinical symptoms of SLE in another phase III trial[277]. Additionally, tocilizumab (IL-6 receptor antagonist) is approved by the FDA for treatment of rheumatoid arthritis and juvenile arthritis[278], although its use has been associated with increased weight gain indicating a potential deleterious effect on MASLD[279]. However, targeting cytokine-driven pathways in

MASLD treatment may prove challenging given that treatment of individuals with NASH using pentoxifylline (phosphodiesterase inhibitor that decreases *TNF* gene transcription) did not significantly improve transaminase levels, liver histology, and metabolic markers compared to the placebo group[280]. Such shortcomings highlight the potential need to target receptor/ligand-driven pathways of immune crosstalk, or possibly to utilize such new approaches in combination with cytokine inhibition.

Preclinical studies that utilize immunotherapies targeting receptor/ligand-driven pathways have also shown promise in inflammatory disease treatment (Table 2). For example, abatacept, which binds to B7.1 and B7.2 with higher affinity than CD28 and blocks T cell activation, is in clinical use for rheumatoid arthritis[281,282], psoriatic arthritis[283], and juvenile idiopathic arthritis[284]. Given the clinical link between these inflammatory arthritic conditions and MASLD[269], whether abatacept, or other pharmacologic agents targeting the CD28/B7 pathway[285], can be efficacious in treating MASLD is yet to be shown. However, abatacept have been suggested to induce hepatocellular damage[286], warranting further cell-specific mechanistic interrogation of the CD28/B7.1&B7.2 signaling pathway in MASLD for its therapeutic exploitation.

Similarly, modulation of 4–1BB/4–1BBL pathway shows promise given blockade of 4–1BB/4–1BBL interaction suppresses inflammation in mouse models of rheumatoid arthritis[287], atherosclerosis[288], and experimental autoimmune myocarditis[289]. However, potential deleterious effects of such interventions should be carefully considered, because 4–1BB deficient mice display altered myeloid progenitor cell growth and reduced adaptive immune responses[290].

Blocking the OX40/OX40L pathway is similarly proven effective in counteracting several inflammatory diseases including asthma[291,292], autoimmune encaphelomyelitis[293], and type 1 diabetes[294] in animal studies (reviewed in [295]). Furthermore, a recent clinical trial revealed that rocatinlimab, an anti-OX40 antibody that blocks OX40/OX40L interaction, is effective in improving atopic dermatitis[296]. Notably, blockade of OX40/OX40L interaction preferentially inhibits effector T cells and restricts widespread immunosuppression. However, the value of therapeutic inhibition of OX40/OX40L axis in MASLD remains unknown.

Targeting CD40/CD40L signaling in mouse models of autoimmune cholangitis via anti-CD40L antibody treatment reduced liver inflammation and lowered autoantibody levels[297]. Further, BI 655064, an antagonistic anti-CD40 antibody that selectively binds to CD40 and blocks CD40/CD40L interaction, improved inflammatory markers in individuals with rheumatoid arthritis[298], invoking a potential beneficial role of CD40/CD40L blockade in inflammatory diseases. The safety, tolerability, and pharmacodynamics of another anti-CD40 antibody, dacetuzumab/lucatumumab, were tested in individuals with primary biliary cirrhosis (Clinical Trial ID: NCT02193360). Although the results have not yet been published, the use of this antagonist in a liver inflammatory disease reinforces the notion that CD40/CD40L axis is a potential candidate for future therapeutic targeting of inflammation in MASLD.

Data on pharmacologic targeting of Fas/FasL signaling is limited, with one preclinical study showing that ONL1204, a small peptide antagonist of Fas, reduces clinical and inflammatory markers in mouse models of glaucoma[299]. Based on these observations, a clinical trial investigating its use for the treatment of age-related macular degeneration, a condition with inflammatory pathogenesis[300], is currently being conducted (Clinical Trial ID: NCT04744662). Whether its use in humans can recapitulate the antiinflammatory effects observed in mice, and its efficacy in countering inflammatory diseases beyond ophthalmic conditions, remain to be investigated.

CD40, OX40, 4–1BB, and Fas are all members of the TNF receptor superfamily (TNFRSF)[301], and despite the apparent potential, targeting other TNFRSF has shown limited clinical efficacy in the context of hepatic inflammation in alcoholic hepatitis[302–304] and chronic hepatitis C[305,306]. Thus, improved understanding of how immune interactions regulate MASLD (e.g., specific cell types, tissues, and stage of disease development that these pathways impact) will aid in development of more efficacious therapies targeting such interactions. Further, given the heterogeneity of human MASLD[54,307], and associated HCC[308], the potential of combining the inhibition of cytokine- and receptor/ligand-driven pathways holds promise for development of personalized therapies.

Conclusion

Vast research endeavors to understand MASLD etiology, pathogenesis, and progression have uncovered the critical involvement of immune cells and inflammatory mediators in disease pathogenesis. Advancements in the field of immunology have enabled further dissection of individual immune components and their respective roles in MASLD pathology. Of note, the bidirectional communication between innate and adaptive immune systems was discovered not so long ago, and the contributions of such communication in MASLD is not yet fully appreciated. Although our discussion regarding innate and adaptive crosstalk was centered around those with activating effects, we acknowledge the potential contributions of those that invoke inhibitory effects (e.g., CTLA-4 [CD152]/B7 family [CD80/CD86][309] and PD-1 [CD279]/PD-L1 [CD274][310]). Though studies have indicated their roles in MASLD[311,312], further work would provide an improved basis for the discussion of potential benefits of limiting low level autoinflammation to restrict MASLD progression.

As more studies begin to interrogate bidirectional immune signaling pathways in MASLD, an exciting new avenue of potential therapeutic approaches has been recognized. Targeting these pathways can be especially effective, allowing both arms of the immune response contributing to disease pathogenesis to be modulated. Improved understanding of how these pathways contribute to MASLD pathogenesis would be required, however, for effective and precise therapeutic strategy. Specifically, some remaining knowledge gaps that will significantly advance the field forward if addressed include definition of: (1) key B and T cell subset(s) involved in the innate-adaptive immune cell crosstalk that drives MASLD pathogenesis, (2) innate immune cell involvement in these interactions, (3) critical liver microenvironment factors that promote or inhibit innate and adaptive immune cell crosstalk, (4) disease stage (e.g., MASH vs HCC[308], early fibrosis vs late cirrhosis[313]; given immunological distinctions[99]) in which these pathways of bidirectional crosstalk play a

significant role, and (5) impact of immune bidirectional crosstalk on MASLD-associated cardiometabolic complications (e.g., portal hypertension[18], CVD[19], T2DM[20]). Finally, given that diet-induced mouse models of MASLD employed by many studies highlighted in this review also simultaneously induce obesity, investigations on the regulatory functions of innate-adaptive bidirectional crosstalk in MASLD pathogenesis may uncover their contributions to other inflammatory sequalae associated with metabolic syndrome.

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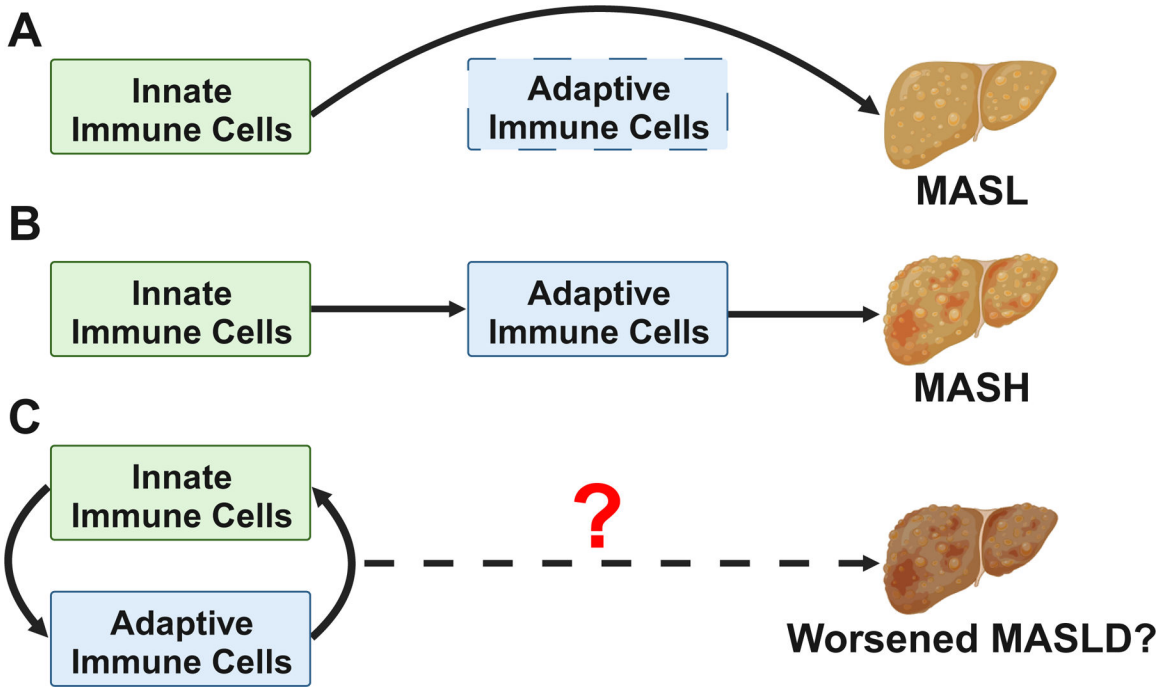

Figure 1. The contribution of innate and adaptive immune systems in MASLD and the role of bidirectional communication between the two arms.

(A) Though the activities of innate immune cells are sufficient to drive the development of metabolic dysfunction-associated steatotic liver (MASL), ablation of adaptive immune cells (e.g., recombination activating 1 [*Rag1*]-knockout in mice) prevents the development of metabolic dysfunction-associated steatohepatitis (MASH). **(B)** Long-appreciated paradigm of MASLD disease progression, in which unidirectional innate activation of adaptive immune cells provides key pathogenic signals to promote the development of MASH. **(C)** Proposed model in which bidirectional immune crosstalk between innate and adaptive immune cells drives full-blown MASLD pathogenesis.

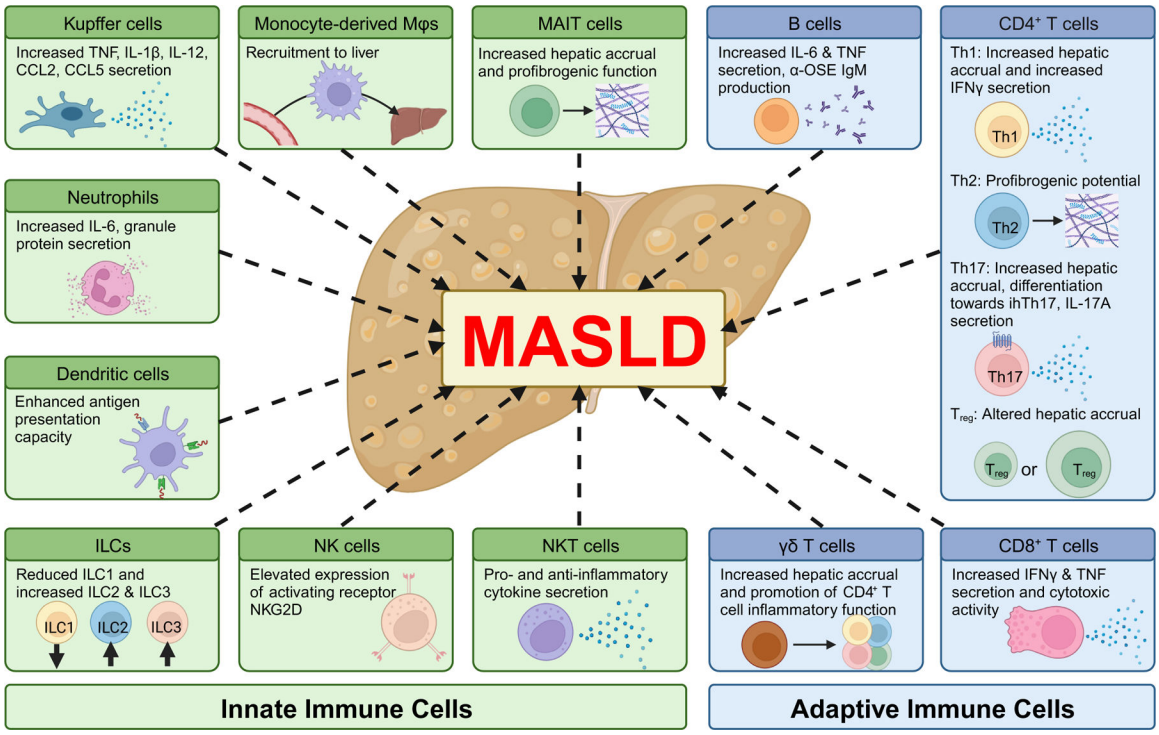

Figure 2. Immunological landscape of MASLD pathogenesis.

Hepatic immune cell function is reshaped during MASLD and contributes to disease pathogenesis. Within innate immune cells, Kupffer cells (KCs) exhibit increased activation leading to increased cytokine and chemokine secretion. However, the MASH environment increases KC death, and in turn the KC population is replaced via increased recruitment of circulating monocytes that differentiate into macrophages. KC activation also recruits neutrophils, which secrete IL-6 and granule proteins to further promote proinflammatory landscape in the liver. Dendritic cells (DCs) exhibit increased hepatic accrual and antigen presentation capacity in MASLD. Contributions of innate lymphoid cells (ILCs) are understudied, with knowledge being limited to changes in hepatic accrual – namely decreased ILC1 and increased ILC2 and ILC3. NK cells express increased level of activating receptor NKG2D and promote activation of other immune cells in the liver by increased secretion of IFNγ. The contributions of NKT cells are disease stage-dependent, secreting both pro and antiinflammatory cytokines that inhibit pathogenesis during early stages but promote disease progression in later stages. Mucosal associated invariant T (MAIT) cells exhibit increased hepatic accrual and proinflammatory/profibrogenic properties, although they have also been associated with suppression of inflammation in MASLD. Of the adaptive immune cells, the contributions of $CD4^+$ T cells are the most studied. Among the canonical proinflammatory subsets, Th1 cells exhibit increased hepatic accrual and IFNγ secretion, and Th17 cells exhibit increased hepatic accrual and IL-17 secretion. Th17 cells are further differentiated towards a highly inflammatory $CXCR3^+$ intrahepatic subset (ihTh17 cells) in MASH. The roles of Th2 and T_{reg} cells are less defined in MASLD. Profibrogenic potential of Th2 cells have been implicated in progression to cirrhosis, while hepatic accrual (and potentially their contributions towards MASLD) of T_{reg} cells varies depending on the disease model. $CD8^+$ T cells secrete more IFNγ and TNF and exhibit

higher cytotoxic activity. γδ T cells show increased hepatic accrual (only in mice) and promote $CD4^+$ T cell function. B cells increase the production of proinflammatory cytokines (IL-6 and TNF) and anti-OSE antibodies.

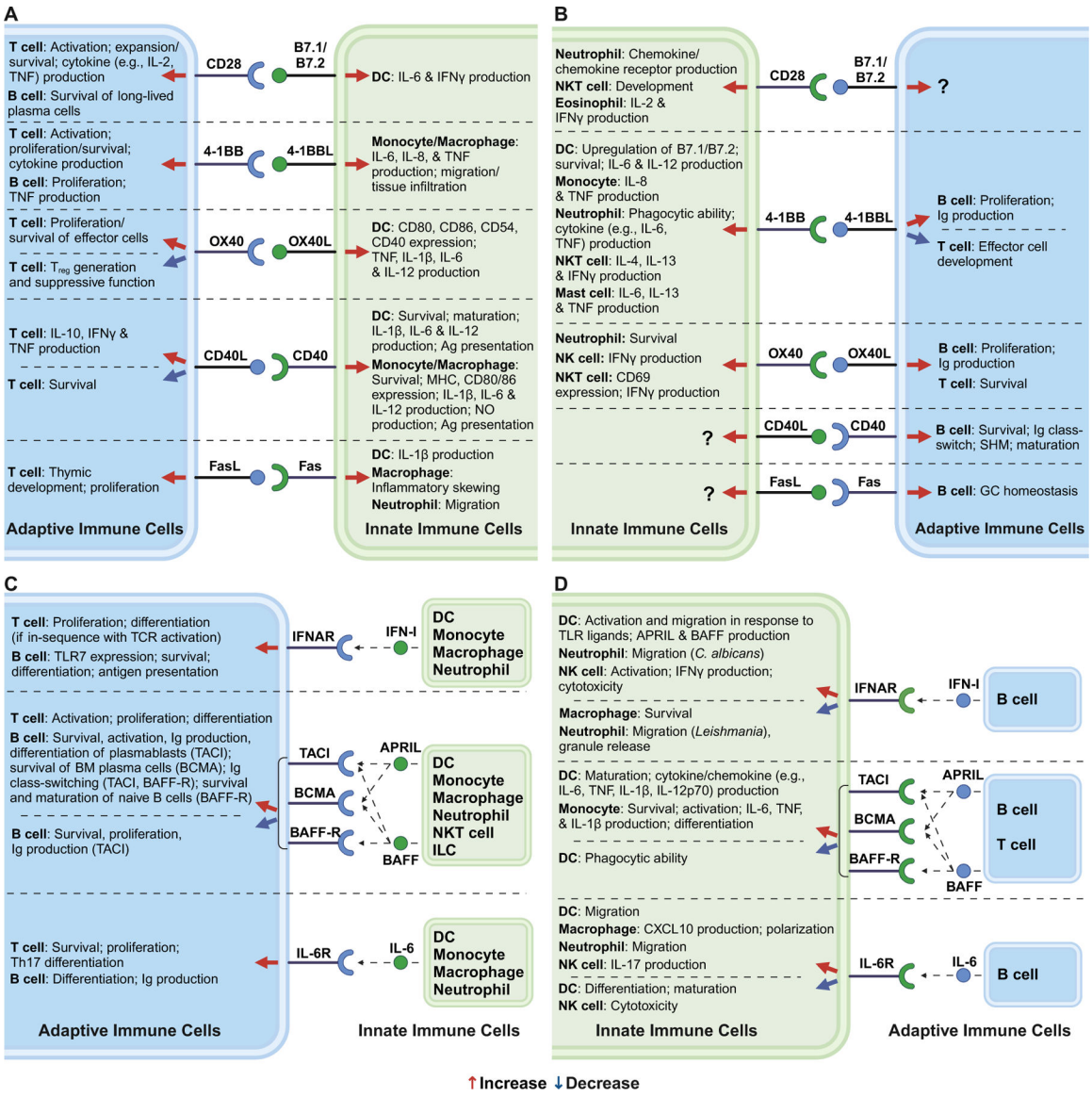

Figure 3. The bidirectional crosstalk between adaptive and innate immune cells and the downstream effects of each signaling pathway.

(A) Canonically appreciated receptor/ligand-driven communication pathways between adaptive and innate immune cells, and “reverse signaling” of these pathways via respective ligands. **(B)** Signaling pathways listed in (A) in which the receptors/ligands are expressed on the opposite arms of the immune system. **(C)** Canonically appreciated cytokine-driven communication pathways between adaptive and innate immune cells. **(D)** Signaling pathways listed in (C) in which the cytokines/receptors are expressed on the opposite arms of the immune system. Red arrow indicates increasing downstream effects. Blue arrow indicates decreasing downstream effects. Receptors, ligands, and cytokines denoted in blue indicate those expressed by adaptive immune cells. Receptors, ligands, and cytokines denoted in green indicate those expressed by innate immune cells. NO, nitric oxide; Ag,

antigen; Ig, immunoglobulin; SHM, somatic hypermutation; GC, germinal center; BM, bone marrow.

Table 1.

Effects of dysregulated immune crosstalk pathways in MASLD mouse models

Pathway	Model used	Diet Fed	Effects on MASLD (compared to WT)	Ref
CD28/B7.1, B7.2	$CD28^{-/-}$ mice (C57BL/6)	HFD (60% kcal fat)	↓hepatic steatosis; ↓hepatic inflammation; ↓hepatocellular damage	181
	$B7.1^{-/-}B7.2^{-/-}$ mice (C57BL/6)	HFD (60% kcal fat)	↑hepatic steatosis; ↑hepatic inflammation; ↓hepatocellular damage	182
	Antibody-mediated depletion of B7.1 and B7.2 in wildtype mice (C57BL/6)	HFD (60% kcal fat)	↓hepatic steatosis; ↓hepatic inflammation	182
4–1BB/4–1BBL	$4–1BB^{-/-}$ mice (C57BL/6)	HFD (60% kcal fat)	↓hepatic steatosis; ↓hepatic inflammation	190
OX40/OX40L	$OX\text{-}40^{-/-}$ mice (C57BL/6)	HFD (45% kcal fat)	↓hepatic steatosis; ↓hepatic inflammation	195
	$Rag2^{-/-}IL2rg^{-/-}$ mice (C57BL/6) adoptively transferred with OX40-deficient T cells	HFD (45% kcal fat)	↓hepatic steatosis; ↓hepatic inflammation	195
CD40/CD40L	$CD40^{-/-}$ mice (C57BL/6)	HFD (55% kcal fat)	↑hepatic steatosis; ↓hepatic inflammation	201, 202
	wildtype mice (C57BL/6) adoptively transferred with $Rag1^{-/-}$ and $CD40^{-/-}$ BM cells	HFD (45% kcal fat)	↑hepatic steatosis	202
	$CD40^{fl/fl}$ CD11c-Cre mice (C57BL/6)	HFD (54% kcal fat)	↑hepatic steatosis; ↑hepatocellular damage; ↓hepatic T_{reg} accrual	200
	$CD40^{fl/fl}$ CD11c-Cre mice (C57BL/6)	NASH diet (40% kcal fat, 20% kcal fructose, 2% kcal cholesterol)	↓hepatic inflammation; ↑hepatocellular damage	200
	$CD40L^{-/-}$ mice (C57BL/6)	HFD (23% kcal fat)	↑↓hepatic steatosis	204, 205
	$CD40L^{-/-}$ mice (BALB/c)	Olive oil administration (6.6 mL/kg of body weight, 3 times/week via oral gavage)	↑hepatic steatosis	203
Fas/FasL	$Fas^{fl/fl}$ Albumin-Cre mice (C57BL/6)	HFD (58% kcal fat)	↓hepatic steatosis	215
IFN-I/IFNAR	$IFNAR1^{-/-}$ mice (C57BL/6)	HFD (60% kcal fat)	↓hepatic steatosis	228
	$IFNAR^{fl/fl}$ Albumin-Cre mice (C57BL/6)	MCD diet	↑hepatic steatosis; ↑hepatic inflammation	229
	$IRF3^{-/-}$ mice (C57BL/6)	HFD (61.6% kcal fat)	↑hepatic steatosis; ↑hepatocellular damage	231
	$IRF5^{flfl}$ Lyz2-Cre mice (C57BL/6)	MCD diet	↓hepatocellular damage; ↓hepatic inflammation; ↓cirrhosis	232
	$IRF5^{flfl}$ Lyz2-Cre mice (C57BL/6)	CCl_4 (0.5 μL/g diluted 1:5 in olive oil; 2 times/week)	↓hepatocellular damage; ↓hepatic inflammation; ↓cirrhosis	232
	$IRF9^{-/-}$ mice (C57BL/6)	HFD (61.6% kcal fat)	↑hepatic steatosis	230
APRIL, BAFF/ BAFF-R, BCMA, TACI	$APRIL^{-/-}$ mice (C57BL/6)	HFD (60% kcal fat)	↓hepatocellular damage	251
	BAFF-transgenic mice (C57BL/6)	HFD (60% kcal fat)	↓hepatocellular damage	251

Pathway	Model used	Diet Fed	Effects on MASLD (compared to WT)	Ref
	BAFF$^{-/-}$ mice (C57BL/6)	HFD (60% kcal fat)	↓hepatic steatosis; ↓hepatic inflammation; ↓cirrhosis	254
	Antibody-mediated neutralization of BAFF in wildtype mice (C57BL/6)	MCD diet	↓hepatic steatosis; ↓hepatic inflammation; ↓hepatocellular damage	157
	TACI-Ig mice (C57BL/6)	MCD diet	↓hepatic inflammation	157
	TACI-Ig mice (C57BL/6)	CDAA diet	↓cirrhosis	157
IL-6/IL-6 receptor	Antibody-mediated neutralization of IL-6 receptor in wildtype mice (C57BL/6)	MCD diet	↑hepatic steatosis; ↓hepatocellular damage	266

HFD, high fat diet; MCD, methionine choline deficient; CDAA, choline deficient and amino acid defined; IFNAR, IFN-I receptor; IRF, interferon regulatory factor; BM, bone marrow. Red upwards arrows indicate augmentation of phenotype. Blue downwards arrows indicate attenuation of phenotype.

Table 2.

Currently available pharmacologic agents with potential to be used for MASLD treatment by targeting pathways of the bidirectional immune crosstalk

Drug Name	Target Pathway	Mechanism of Action	Effects on Inflammatory Disease	Ref
Abatacept	CD28/B7.1, B7.2	CTLA4-Ig: prevention of T cell activation by blocking B7 binding to CD28	Reduces inflammation in various forms of arthritis	281-284
Rocatinlimab	OX40/OX40L	antiOX40 antibody: inhibition and reduction of activated OX40-expressing T cells	Progressive improvements in atopic dermatitis	296
BI 655064	CD40/CD40L	antiCD40 antibody: blockade of CD40/CD40L interaction	Improvement of clinical and biological markers of rheumatoid arthritis	298
IFN-α kinoid	IFN-I/IFNAR	Immunotherapeutic vaccine: induction of generation of IFN-neutralizing antibodies	Improvement of clinical signs/symptoms in SLE	276
Anifrolumab	IFN-I/IFNAR	IFNAR/IFNBR blocking antibody: blockade of IFNAR signaling	Improvement of clinical signs/symptoms in SLE	277
Tocilizumab	IL-6/IL-6 receptor	IL-6 receptor antagonist: blockade of IL-6 receptor signaling	FDA approved to treat rheumatoid arthritis and juvenile arthritis	278
Pentoxifylline	TNF/TNF receptor	Phosphodiesterase inhibitor: suppression of TNF gene expression	Improvement of liver enzymes and insulin resistance, and reduction in steatosis and lobular inflammation, in NASH	280

SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.