Monocyte dysregulation: consequences for hepatic infections

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Abstract
Liver disorders due to infections are a substantial health concern in underdeveloped and industrialized countries. This includes not only hepatotropic viruses (e.g., hepatitis B, hepatitis C) but also bacterial and parasitic infections such as amebiasis, leishmaniasis, schistosomiasis, or echinococcosis. Recent studies of the immune mechanisms underlying liver disease show that monocytes play an essential role in determining patient outcomes. Monocytes are derived from the mononuclear phagocyte lineage in the bone marrow and are present in nearly all tissues of the body; these cells function as part of the early innate immune response that reacts to challenge by external pathogens. Due to their special ability to develop into tissue macrophages and dendritic cells and to change from an inflammatory to an anti-inflammatory phenotype, monocytes play a pivotal role in infectious and non-infectious liver diseases: they can maintain inflammation and support resolution of inflammation. Therefore, tight regulation of monocyte recruitment and termination of monocyte-driven immune responses in the liver is prerequisite to appropriate healing of organ damage. In this review, we discuss monocyte-dependent immune mechanisms underlying hepatic infectious disorders. Better understanding of these immune mechanisms may lead to development of new interventions to treat acute liver disease and prevent progression to organ failure.

Keywords Monocytes • Infection • Inflammation • Hepatic disorder

Background
Due to its high degree of vascularization, the liver functions as a blood-cleansing “sieve,” which is exposed constantly to foreign or self-antigens such as pathogens, toxins, and cell debris; therefore, the organ plays an initial role in balancing and limiting inflammatory responses [1, 2]. To facilitate this, the liver contains large numbers of transient or permanently resident, highly specialized, and effective innate immune cells [3]. First and foremost are intra-sinusoidal macrophages called Kupffer cells (KCs), which have a high capacity for phagocytosis and recognize self or foreign antigens, such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), released by necrotic cells [4]. KCs capture circulating bacteria from the bloodstream, as demonstrated for their ability to clear *Staphylococcus aureus* bacteremia [5]. Activation of KCs leads to release of chemokines and to activation as well as recruitment of lymphoid- or myeloid-derived innate immune cells such as natural killer cells, natural killer T cells, neutrophils, and monocytes [3, 6–8]. In contrast to other effector cells, monocytes, which are derived from hematological progenitors in the bone marrow, move to the site of injury or infection via the blood stream and exert multiple functions. For example, these cells can give rise to self-renewing, tissue-resident KCs, which were previously assumed to develop exclusively from embryonic precursor cells [9], as well as tissue-specific macrophages and dendritic cells (DCs) [10]. In addition, these cells are critical for defense against microbial infections and for promoting resolution of inflammation; however, while exerting these actions, they can cause profound collateral damage to host tissues by perpetuating inflammation and promoting fibrosis [8, 11–13].

Accordingly, monocytes represent a unique cell population capable of exceptional plasticity since they can act both as precursors of KCs and as effector cells; they can even switch...
from one state to another by undergoing marked phenotypic and functional changes [14, 15]. Monocytes and monocyte-derived macrophages are characterized by two major functions. On the one hand, they eliminate pathogens by phagocytosis, release active compounds such as reactive oxygen species, secrete pro-inflammatory cytokines, and modulate T-cell-mediated immune response via antigen presentation [16]. On the other, they are key players in tissue and wound healing reactions because they initiate, maintain, and resolve tissue repair processes [4]. In mice, monocytes are divided into two major subsets: classical (which exhibit pro-inflammatory and antimicrobial properties) and non-classical (which exhibit anti-inflammatory properties and mediate reparative and antiviral mechanisms) [17].

Monocytes are differentiated according to expression of specific surface markers and receptors, which differ between the most investigated species, mice and humans. In mice, classical monocytes express CD11b, high levels of Ly6C, and the CC chemokine receptor 2 (CCR2), but low levels of CX3C chemokine receptor 1 (CX3CR1) [18]. Even though CX3CR1 expression was commonly used as additional marker for classical and non-classical monocyte discrimination in mice, a recent publication demonstrated that both cell types exhibit equal CX3CR1 protein expression level on the surface [19]. This discrepancy was referred to the use of mice which express EGFP in monocytes a.o. under control of the endogenous CX3CR1 locus [20]. EGFP-positive cells should be considered cells that expressed CX3CR1 within the half-life of EGFP (>24 h). This implies that current surface expression of CX3CR1 is not correlated proportionally with EGFP fluorescence and the historically common discrimination of murine classical and non-classical monocytes with the help of CX3CR1 surface expression should reconsidered [19].

Classical monocytes, which represent approximately 2–5% of circulating white blood cells, are referred to as Ly6C hi monocytes. The non-classical subset of circulating monocytes in mice is slightly less abundant; this subset expresses low levels of Ly6C and high levels of CD43 [12, 19]. In humans, monocyte subsets are divided into three groups according to expression of CD14, the co-receptor for toll-like receptor (TLR) 4 (which recognizes bacterial lipopolysaccharides) [21], and CD16 (also known as FcyRIII) [22]. In addition to CCR2, the human equivalent of classical monocytes is classified as CD14 hi and CD16, and non-classical monocytes are defined as CD14+CD16+ and do express higher level of CX3CR1 compared to classical human monocytes [23]. The third subset in humans is a CD14+CD16+ intermediate population with pro-inflammatory properties [23]. Studies show that there seems to be an intermediate (Ly6C mid/low) monocyte subpopulation in mice as well. Detailed genomic characterization revealed that C/EBPβ drives conversion of Ly6C hi monocytes to Ly6C ch monocytes via Ly6C mt monocytes, which are more heterogenous than the already known populations [15]. Furthermore, studies in a model of sterile hepatic injury in mice which express EGFP under control of the endogenous CX3CR1 locus and RFP under the control of CCR2 locus suggest that CCR2 ch classical monocytes transition into CX3CR1 hi monocytes and that this conversion is essential for the role of non-classical Ly6C lo monocytes in ensuring proper tissue repair [24].

Generally, it is accepted that the function of the different monocyte subsets is conserved across species. However, comparison of gene expression profiles between mouse and human monocyte subsets by microarray analysis revealed differences in expression profiles [25]. The use of advanced methods such as fate mapping and single-cell RNA sequencing to decipher population dynamics and functional differences between monocytes suggests that, beyond the historical classification into classical, intermediate, or non-classical subsets, many more subsets might exist [16]. Most recently, a study in a murine model of multiple sclerosis (experimental autoimmune encephalomyelitis) identified at least eight different monocyte subsets by single-cell RNA sequencing [26].

Egress and tissue recruitment of classical monocytes is highly dependent on the surface receptor CCR2, which binds to C-C chemokine ligand 2 (CCL2; also known as MCP1) or CCL7 (also known as MCP3) [11, 27]. Many liver cells are capable of expressing CCL2 and, to a lesser extent, CCL7, and high expression levels are observed in the circulation during infectious or sterile inflammatory conditions [27–29]. Despite different approaches, the exact roles played by CCL2 and CCL7 in recruitment of monocytes are unclear; however, we do know that lack of expression leads to a significant reduction in monocyte numbers during infection [12, 27, 28].

Generation of mice harboring a deletion in the ccr2 gene (Ccr2+/- mice) allowed to study the actual role of monocytes in different disease settings [30]. Ccr2+/- mice harbor reduced numbers of classical circulating blood monocytes and show impaired monocyte recruitment to various tissues during inflammation; this is concomitant with an increased monocyte population in the bone marrow [27, 30]. The latter finding appears to be due to a defect in adhesion to the vascular endothelium, which inhibits extravasation from the bone marrow [31]. Using this mouse model, the pivotal role of monocytes in different diseases was depicted clearly. On the one hand, they were essential for control and clearance of microbial infections and for resolving inflammatory conditions; however, they also contributed to the pathogenesis of certain infections, drug-induced toxicity, and chronic inflammatory and degenerative diseases [12, 32]. Monocyte-mediated protective and anti-inflammatory responses are seen in many cases of bacterial, parasitic, and viral infections, including listeriosis, tuberculosis, toxoplasmosis, cutaneous leishmaniasis, and malaria [33–37], as well as in cases of herpes simplex and West Nile virus infection.
However, more and more infection-related diseases have been identified in which monocytes contribute to immunopathology; examples include murine models of protozoan infections such as trypanosomiasis and hepatic amebiasis, human viral infections such as influenza, SARS-CoV, or SARS-CoV2, and human viral infections such as influenza, parainfluenza, and rhinovirus. The ability of monocytes to induce tissue damage results from their primary role in defense against invading pathogens, for which they are equipped with a number of strong effector mechanisms; these include secretion of matrix metalloproteinases capable of degrading extracellular matrix components, a high capacity for phagocytosis and antigen presentation, release of nitric oxide (NO), reactive oxygen species (ROS), pro-inflammatory cytokines (tumor necrosis factor α (TNF), interleukin (IL)-6, IL-8, and IL-1β), chemokines (CCL1, CCL2, CCL3, and CCL5), and secretion of growth factors (granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) In particular, production of chemokines such as CXC motif ligand 1 (CXCL1; also known as GRO-α oncogene or neutrophil-activating protein 3) can lead to further recruitment of innate immune cells, which maintain the inflammatory process. However, monocytes do not act independently; rather, they are closely associated with activation and polarization of resident macrophages in damaged tissues. Also, as for monocytes, the traditional categorization of macrophages as pro-inflammatory (M1) or anti-inflammatory/tissue repairing (M2) is called into question by new methodologies; a more comprehensive phenotypical description is needed to describe macrophages in different disease settings. For instance, the environment of a diet-induced fatty liver imprints a unique inflammatory signature on various myeloid hepatic cell populations that has features of M1 as well as M2 polarization. Nevertheless, liver macrophages are within the first line of defense against foreign or self-derived challenges, and as such they respond flexibly to signals arising from circulating blood and immune cells. Furthermore, their potential to secrete an armada of immune cell-activating cytokines and chemokines puts them in a position to recruit circulating monocytes to control inflammation, repair tissues, and terminate the inflammatory response, thereby controlling the different stages of liver injury. When the homeostasis of this hepatic system is disturbed, profound immunopathological states, which may lead to severe liver dysfunction, cirrhosis, and fibrosis (which require highly demanding treatment and development of new treatment strategies), can occur. Below, we describe the immunopathological role of monocytes during development of liver-specific infections by different pathogens, including parasites, bacteria, and viruses (Fig. 1). The information provided will consolidate our knowledge of monocyte-induced immunopathologies.

Infectious microbial challenges affecting the liver

Infectious agents such as protozoan/parasites, bacteria, and viruses can have various effects on the liver. Clinical manifestations range from asymptomatic, characterized by transient increases in aminotransaminases, to massive liver destruction, fibrosis, and development of primary liver tumors. Immunological mechanisms underlying many infection-related diseases of the liver are, for the most part, incompletely understood. For this reason, we review a selection of infection-related liver diseases and focus on those for which involvement of monocytes in development of liver damage has been investigated.

Monocyte dysfunction during parasitic infections

There are two main classes of parasite: unicellular protozoa and multicellular helminths. Both can cause serious disease in humans during different stages of development. Among the most important protozoa that have the potential to damage the liver are vector-borne pathogens such as Leishmania or trypanosomes, and intestinal parasites such as the protozoan Entamoeba (E.) histolytica. The second group includes large helminths such as tapeworms, known as cestodes (e.g., Echinococcus multilocularis), or flatworms such as Schistosoma (e.g., Schistosoma mansoni), both of which can cause life-threatening liver disease in humans. Dysregulated and overwhelming inflammation is a major cause of pathogenicity during parasitic infections. Although many studies highlight the role of monocytes in host defense against parasites, only a few have investigated the contribution of monocytes to parasite-mediated liver damage. This is due, at least in part, to the lack of suitable animal models for complex organisms such as parasites, which are highly adapted to their host.

Hepatic amebiasis

Invasive amebiasis is caused by oral infection with the environmental-resistant cyst stage of the protozoan parasite E. histolytica, which is still a serious health problem in developing countries with poor sanitary conditions; it is also a concern for returning travelers and immigrants. Initially, the intestine is asymptomatically colonized by motile trophozoites, which develop from environment-resistant cysts. Virulence factors expressed by trophozoites, including surface lectins, cysteine peptidases, and pore-forming peptides, enable the parasite to penetrate the mucous membrane wall and induce hemorrhagic diarrhea; the parasite then spreads via the bloodstream to other organs, especially the liver. Liver manifestation is characterized by progressive destruction of liver tissue, resulting in amebic liver abscess, which occurs...
predominantly in adult men [61]. Several rodent models mimic the liver lesions observed in humans, which are characterized by a central necrotic zone surrounded by a trophozoite layer and a ring of inflammatory cells that delimit the abscess from the liver tissue [62]; however, most studies are hampered by a lack of tools suitable for studying the immunological mechanisms underlying abscess development. An immunocompetent murine model of the disease exhibits high similarity to hepatic amebiasis in humans; however, in contrast to humans, mice are able to control abscess development [63]. Primary histological and immunological studies using this model reveal massive infiltration by immune cells, mainly monocytes and neutrophils, and an increase in expression of CCL2 mRNA and protein in the liver at early time points post-intrahepatic infection with axenically cultured trophozoites [40, 63]. CCL2 expression and monocyte recruitment in this infection model is dependent on initiation of the IL-23/IL-17 axis [64]. Although this axis is involved in protection against several pathogens [65, 66], infection-induced pathological changes can occur after activation [67]. Depletion of CD11b+ Ly6C+ monocytes and neutrophils from wild type mice using Gr1- and Ly6G-specific monoclonal antibodies significantly reduced abscess formation, and liver damage was virtually eliminated [40]. Depletion of liver-resident macrophages by clodronate-loaded liposomes abrogated abscess formation, and depletion of TNF (which is also secreted by Ly6C+ monocytes) revealed that this cytokine is mainly responsible for tissue damage [40]. In addition to TNF, expression of CCL2 and the chemoattractant CXCL1 by Ly6C+ monocytes increased during E. histolytica infection [48]. Furthermore, surface molecules expressed by E. histolytica might contribute to activation of monocytes and macrophages. Previous in vitro studies show that the Gal/GalNAc lectin (Gal-lectin) activates the NF-kB and MAP kinase-signaling pathways in murine macrophages, resulting in upregulation of mRNAs encoding cytokine and receptor genes involved in pro-inflammatory responses [68, 69]. The interaction between another highly immunogenic surface molecule and pathogenicity factor expressed by E. histolytica (a lipopeptidophosphoglycan) [70, 71] and TLR2 and TLR4 led to release of IL-10, IL12p40, TNF, and IL-8 by human monocytes, again via activation of NF-kB [47]. IL-8, also known as CXC motif ligand 8 (CXCL8), is a member of the CXC chemokine family that binds to target cells expressing the CXCR1 or CXCR2 receptors, thereby inducing chemotaxis of innate immune cells such as neutrophils and monocytes to sites of infection or injury [72], also contributing to angiogenesis and liver damage [73]. Very closely related to the
functions of CXCL8 are those of CXCL1 [74]. Binding of CXCL1 to its specific receptor CXCR2 leads to recruitment of neutrophilic granulocytes and monocytes into inflamed or injured tissues [75, 76]; it also promotes inflammatory processes via regulation of the NLRP3 inflammasome [77]. In *E. histolytica* liver infection, depletion of CXCL1 reduces tissue damage, which is paralleled by diminished recruitment of Ly6C<sup>hi</sup> monocytes [48].

Moreover, TNF stimulates expression of NADPH oxidase via activation of NF-kB pathways in monocytic cells. Activation of NADP(H) oxidase can lead to generation of superoxide anions, which form oxidants such as hydroxyl radicals (OH•) or hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in combination with water [78]. Together with the production of nitric oxide by macrophages, these effectors are highly toxic to amebic trophozoites *in vitro* [79]. However, the parasite is equipped with specific enzymes that allow detoxification of oxygen and nitrogen intermediates [80], and it even expresses an arginase that competes with inducible NO synthase for its substrate [81]. Given these abilities of *E. histolytica* to respond to monocyte/macrophage-mediated defense mechanisms, it seems possible that immune effector molecules may react against host tissues rather than against the parasite. Indeed, depletion of TNF using a specific monoclonal antibody reduces abscess size in the mouse model of amebiasis [40].

Interestingly, expression of TNF and CXCL1 was higher in monocytes from male individuals than in those from females; this applied to both Ly6C<sup>hi</sup> monocytes in the murine model of amebiasis and CXCL1 in LPS-stimulated CD14<sup>++</sup>CD16<sup>-</sup> monocytes from healthy human subjects [48]. Moreover, expression of TNF, CCL2, and CXCL1 by Ly6C<sup>hi</sup> monocytes in the murine model for hepatic amebiasis is increased by testosterone treatment, and expression of TNF and CXCL1 by LPS-stimulated PBMCs from women undergoing testosterone treatment increases while they undergo gender transition [48]. The effect of sex is also observed for CCL2. Serum levels of CCL2 in men intestinally infected with *E. histolytica* are significantly higher than those in women [29]. In addition, transcriptomic data from stimulated human monocytes from both sexes reveals a stronger expression profile for genes associated with monocyte migration, chemotaxis, and motility in men [48].

Repair of liver damage after parasite infection has been investigated in the murine model for hepatic amebiasis; data suggest that repair can be attributed to Ly6C<sup>ch</sup> monocytes, thereby paralleling observations from repair processes after sterile liver fibrosis [82]. A rapid and significant increase in regenerative IL13- and Arg1-releasing Ly6C<sup>ch</sup> monocytes upon infection was identified as being involved in abscess recovery [64].

Overall, the data suggest that hepatic amebiasis, which occurs predominately in men, is largely dependent on recruitment of monocytes and monocyte/macrophage-mediated immune activation triggered by testosterone.

**Leishmaniasis**

Leishmaniasis is a vector-borne, wide-spread disease caused by intracellular infection with a protozoan parasite; this disease has three main variants: cutaneous (CL), mucocutaneous (MCL), and visceral leishmaniasis (VL). The latter is a severe systemic parasitosis induced by *Leishmania (L.) donovani* and *L. infantum* [83]. *Leishmania* parasites survive within phagocytic cells such as neutrophils, monocytes, and macrophages and then spread to the spleen, liver, and bone marrow [84]. In the liver, *L. donovani* preferentially infects KCs and macrophages derived from circulating inflammatory monocytes [85]. Protective immunity against VL is mediated by a strong Th1 immune response, characterized by activation of the IL12-IFNγ-inducible (i)NOS pathway triggered by dendritic cells [86]. Interestingly, mice lacking STAT1, an important transcription factor for Th1 signal transduction, are resistant to infection with *L. donovani*, suggesting that additional immune factors are involved in protection [87]. Later on, it was shown that adoptive transfer of wild-type Ly6C<sup>hi</sup> monocytes to *L. donovani*-infected STAT1<sup>−/−</sup> mice restores the original phenotype of C57BL/6 WT mice [85]. Blocking recruitment of inflammatory monocytes using the CCR2 antagonist RS-504393 leads to a significant reduction in the parasite load in the liver. This was paralleled by a reduction in IFN-γ/IL10-producing CD4<sup>+</sup> T cells [85]. This immunopathology could be counteracted by IL-17 production of γδ T cells, which are recruited to the liver during *L. donovani* infection and exert a suppressive effect on CCR2<sup>+</sup> monocytes [88]. Not only in VL but also in CL caused by *L. braziliensis*, the increased frequency of intermediate CD14<sup>++</sup>CD16<sup>−</sup> monocytes producing TNF and IL-1β is associated with tissue damage and immunopathology in humans [89, 90]; interestingly, as in amebiasis, infection rates and disease severity caused by the above-mentioned *Leishmania* species are more prominent in men [91].

**Trypanosomiasis**

African trypanosomes are extracellular protozoan parasites that cause sleeping sickness in humans and Nagana disease in cattle in sub-Saharan Africa. Experimental murine models are used to study infection-associated liver pathology of the causative protozoans, *Trypanosoma (T.) brucei* and *T. congolense*, respectively [92]. In both models, protection requires IFNγ-dependent activation of classically activated monocyteic cells and production of trypanotoxic effector molecules such as TNF and/or NO [92]. Overproduction of these effectors by persistent infection leads to liver cell necrosis by TNF- and iNOS-producing DCs (Tip-DCs). These inflammatory Tip-DCs develop either directly from Ly6C<sup>hi</sup> monocytes or via a maturation step that involves IFNγ and MyD88 signaling [39]. Hence, CCL2/CCR2-dependent recruitment of...
Ly6C\textsuperscript{hi} monocytes from the bone marrow is a requirement for induction of liver damage, and, accordingly, the absence of CCR2 signaling reduces liver pathogenicity and prolongs survival of *T. brucei*-infected mice [39]. Although CCR5 and macrophage migration inhibitory factor (MIF), two other recruitment factors, were detected on monocytes during murine *T. brucei* infection, it was shown that these factors are not necessary for the emigration of classical monocytes from the bone marrow but promote their migration to the liver [39]. Especially, MIF increases recruitment of inflammatory monocytes and neutrophils and mediates pathogenic inflammatory immune responses during murine *T. brucei* infection [93]. Interestingly, IL-10 plays a major role in *T. brucei* infection. The depletion of IL-10, either using *Il10\textsuperscript{-/-}*, mice or through treatment with an antibody specific for the IL-10R, increased expression of CCL2 mRNA and protein, along with the frequency of Ly6C\textsuperscript{hi} monocytes; this led to exacerbation of pathogenicity [39, 94]. Consequently, IL-10 inhibits differentiation of monocytes to Tip-DCs and protects the host from tissue damage [94]. In summary, as in amebiasis and leishmaniasis, the imbalance between host protection and hepatic tissue damage caused by trypanosome infection is mediated by Ly6C\textsuperscript{hi} monocytes.

### Schistosomiasis

Schistosomiasis is an often neglected tropical disease caused by infection with helminths belonging to the genus *Schistosoma*, especially *Schistosoma (S.) mansoni*, and others [95]. Humans are infected by free-swimming cercariae, which penetrate the skin and migrate to the liver, where young and mature worm stages provoke unspecified reactive hepatitis. Eggs, which are released in the liver parenchyma, trigger an immune response that results in chronic granulomas and periportal fibrosis [96]. These granulomas are characterized by dense accumulation of innate immune cells and cells belonging to the adaptive arm of the immune response.

The murine infection model for the disease is characterized by CCL2/CCR2-dependent recruitment of Ly6C\textsuperscript{hi} monocytes to the liver, and an increase in granuloma-associated resident CX3CR1\textsuperscript{hi} macrophages. Pulse-chase BrdU labeling revealed that most of the macrophages in the infected liver arise from recruited Ly6C\textsuperscript{hi} monocytes; also, deletion of monocytes (using CCR2-DTR mice) resulted in reduced granuloma formation but exacerbated disease pathogenicity [97].

Peripheral monocytes, which are recruited to the site of infection, produce TGF-\(\beta\) and differentiate into monocyte-derived CX3CR1\textsuperscript{hi} macrophages, which become alternatively activated due to IL-4/IL-13 signaling via IL-4R\(\alpha\). This type of macrophage is further characterized by transcription of *Arg1*, *Chi3L3*, *Relma*, and *Mrc1*, which is coordinated by STAT6 [98]. Furthermore, these macrophages are potent producers of pro-fibrinogenic cytokines such as IL-10 and TGF-\(\beta\). Interestingly, it seems that recruited Ly6C\textsuperscript{hi} monocytes during schistosomiasis transition directly into alternatively activated macrophages without first adopting the phenotype of Ly6C\textsuperscript{hi} monocytes [98]. However, Ly6C\textsuperscript{hi} and intermediate Ly6C cells also contribute to pathogenicity; indeed, reduced hepatic accumulation observed in mice with reduced expression of CD18 (\(\beta_2\) integrin receptor subunit) results in increased formation of granulomatous lesions in the liver, increased egg deposition, and increased mortality [99].

Studies in human patients with incipient or severe fibrosis show high expression of HLA-DR, TGF-\(\beta\), IL-6, and TNF, and reduced expression of anti-fibrotic IL-12, by CD14\textsuperscript{+}CD16\textsuperscript{-} and CD14\textsuperscript{+}CD16\textsuperscript{+} monocytes [96]. This suggests that, analogous to mice, classical monocyte subsets contribute to the pool of alternatively activated macrophages, and hence to liver fibrosis. Indeed, monocyte therapy reduces liver fibrosis induced by *S. mansoni* infection in experimental settings, mainly due to a decrease in production of inflammatory and pro-fibrogenic mediators. In addition, monocyte infusion caused downregulation of factors associated with pro-inflammatory macrophages, as well as upregulation of markers associated with alternatively-activated monocytes. These findings reinforce the hypothesis that a predominance of alternatively activated macrophages may favor improvement of hepatic fibrosis in a preclinical model through fibrous tissue remodeling and modulation of the inflammatory response and fibrogenesis [100].

Given that monocytes from males show a stronger pro-inflammatory profile than those from females due to higher testosterone levels [48], and that testosterone is protective in a murine model of schistosomiasis [101], it can be assumed that monocytes play a central role in the immunopathology of *S. mansoni* infection in a sex-dependent manner.

### Echinococcosis

Infections caused by the cestode *Echinococcus (E.) granulosus* lead to development of hydatide cysts in the liver, which can result in chronic cholangitis or liver cirrhosis [57].

Antigen B (EgAgB), an abundant lipoprotein released by the larvae of *E. granulosus*, is a potential ligand for monocyte and macrophage receptors [102]. Ligation of EgAgB inhibits PMA/LPS-mediated secretion of IL-1\(\beta\) and TNF\(\beta\) by THP1 cells; it also induces a modest arginase-I response and triggers differentiation towards an alternative activation-like phenotype. This type of signal transmission could limit TLR4-mediated pro-inflammatory cytokine production by extracellular matrix proteins, which occurs during the growth of cysts, leading to immune evasion by the parasite [103]. By contrast, recruited monocytes in mouse models of potentially fatal liver infection by *E. multilocularis* are characterized by high production of TNF and caspase 3; TUNEL staining reveals...
significant apoptosis, which may suppress the host antiparasitic immune response [104].

Toxoplasmosis

The tachyzoite stage of the protozoan Toxoplasma (T.) gondii can manifest in the liver as giant-cell hepatitis or non-specific reactive hepatitis, especially in immunocompromised hosts in whom an infection exacerbates chronic latent infections [57]. However, in contrast to the protozoan infections described above, experimental murine studies suggest that recruitment of Ly6C\textsuperscript{hi}, but not neutrophils, contributes to protection from toxoplasmosis, and impaired emigration of monocytes results in severe inflammation and loss of parasite control [105]. Protection is mediated by TNF- and iNOS-producing cells, which differentiate from monocytes recruited to the lamina propria in a CCR2-independent manner [35]. Furthermore, recruited monocytes dampen neutrophil-mediated tissue damage by producing prostaglandin E2 and IL-10 [106]. Also, T. gondii profilin (TgPRF), a TLR11 ligand, promotes recruitment of Ly6C\textsuperscript{hi}CCR2\textsuperscript{+} inflammatory monocytes and even confers resistance to co-infection by bacteria such as Listeria monocytogenes [107].

Interestingly, T. gondii-induced immunopathology in the gut is mediated by IL-23, but unlike amebiasis, matrix metalloproteinase-2 and IL-22 (not further activation of the IL-23/IL-17 axis or CCL2-dependent recruitment of monocytes) is essential for tissue damage [108].

Taken together, these parasitic diseases are accompanied by an unbalanced monocytic immune response. In most cases, monocyte recruitment is induced by the CCL2/CCR2 axis, and immunopathology is often triggered by the release of TNF. Due to the scarcity of primary liver tissue from infected patients, the role of monocytes is mostly elucidated in immunocompetent mouse models, so far. In addition, all of these infections suffer from the fact that they are classified as neglected diseases that occur in low-income populations in developing countries.

Monocyte dysfunction during bacterial infections

Mononuclear phagocytes, including the tissue-resident KCs in the liver, contribute to antibacterial defense mechanism. For instance, they clear blood-circulating bacteria followed by intracellular bacterial killing; in cases of insufficient bactericidal activity, they can also serve as reservoirs for further bacterial spreading [109, 110]. In general, the Ly6C\textsuperscript{hi} monocytes are less likely to trigger immunopathological events in response to bacterial liver infections than in response to parasitic or viral infections. However, such reactions can occur.

Listeria monocytogenes

Infection with Listeria (L.) monocytogenes, a gram-positive, intracellular bacterium, leads to recruitment of inflammatory cells to the liver and spleen and to formation of liver microgranuloma. Tip-DCs derived from Ly6C\textsuperscript{hi} monocytes contribute to innate defense against L. monocytogenes; hence, infection is worse in mice deficient in CCL2 and CCL7 [11] or in Ccr2\textsuperscript{-/-} mice due to an increased bacterial burden. Furthermore, T-cell activation in response to L. monocytogenes infection is not hampered in the absence of Tip-DCs [33]. Moreover, hepatic TLR2 signaling promotes release of CCL2 and CXCL1 upon L. monocytogenes infection, leading to increased motility of monocytes and macrophages, which results in liver microgranuloma formation [111].

Salmonella

The intestine is a major target for Salmonella spp.; however, this gram-negative bacteria species can spread to other organs and, occasionally, to the liver. Although liver-specific infection studies in mice are rare, data suggest that the enteric phase of infection is characterized by immunopathology mediated by iNOS-producing inflammatory monocytes. Like other enteropathogenic bacteria, Salmonella is equipped with type-three secretion systems (T3SS)-1 and T3SS-2. A recent study shows that these complexes interfere with and promote CCL2/CCR2-dependent recruitment of inflammatory monocytes and tissue damage. Pathology and bacterial growth are abolished in CCR2\textsuperscript{-/-} mice, suggesting that monocytes might serve as a niche for Salmonella, as observed for Leishmania [112].

Yersinia enterocolitica

Infections with Yersinia enterocolitica are not restricted to the gastrointestinal tract and mesenteric lymph nodes; they also affect the liver. Although monocyte-derived CD11c\textsuperscript{+} DCs are essential for priming a protective CD8 T-cell response to this infection, mice lacking CCR2 show better survival, reduced weight loss, and increased clearance of Yersinia from the mesenteric lymph nodes. This correlates with reduced expression of Ly6C\textsuperscript{hi} in the periphery, and by increased numbers of neutrophils in the liver [113]. In this case, monocytes may play a dual role: on the one hand, they are involved in establishing a protective immune response, but they may also contribute to immunopathology. However, further detailed experiments are needed to clarify these conflicting results.

In conclusion, several studies report an imbalanced or dysregulated innate immune response to bacterial infection; however, there is a general lack of information about the detailed role of monocytes as a possible cause of immunopathology during responses to these infections.
**Monocyte dysfunction during viral infections**

As with certain protozoan or bacterial pathogens, infection by viruses may also lead to manipulation and utilization of monocytes/macrophages for dissemination, long-term persistence within tissues, and replication. Moreover, there are also specialized viruses that specifically infect parenchymal cells of the liver, including hepatocytes.

**Dengue virus**

The mosquito-transmitted *Dengue virus* (DENV), a positive-stranded RNA virus belonging to the family *Flaviviridae*, has four serotypes that cause up to 96 million cases annually; symptoms range from mild febrile episodes to a severe hemorrhagic course that may be accompanied by acute liver failure [56, 114]. In addition to monocytes and immature monocyte-derived DCs, the virus itself and viral antigens can be detected in hepatocytes and KCs, suggesting that these cells support viral replication and contribute to liver injury [114, 115]. The severe course of DENV infections is characterized by endothelial damage and vascular leakage, which results from PAMP/DAMP-mediated production of IL-1β and TNF by DCs and monocytes [116]. Different subsets of monocytes play an important role in immunopathology, leading to the severe disease outcomes. Studies in humans reveal that infection with DENV reduces both the number and frequency of non-classical CD14+CD16++ monocytes, which produce TNF and show a more activated phenotype than cells from healthy controls. Furthermore, these non-classical monocytes show decreased expression of CD16, along with an increased expression of CD64, CD86, CCR2, and CCR5, while CX3CR1 is reduced upon DENV infection [117]. A recent study shows that DENV infection increases expression of TLR2 by peripheral monocytes which, together with CD14 and TLR6, promote expression of inflammatory cytokines. As a result, vascular permeability increases, paving the way for the severe progressive form of the disease [116].

**Hepatitis B/hepatitis C (HBV/HCV)**

Infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the most important causes of hepatitis and chronic liver disease worldwide [118, 119]. The disease course of HBV and HCV differ with respect to immune responses, leading to distinct clinical outcomes. Infection with the DNA virus HBV, which belongs to the *Hepadnaviridae* family, can be controlled in humans (either naturally or by use of antivirals), but it persists for a lifetime. HCV is a positive-stranded RNA virus belonging to the *Flaviviridae* family; it is a highly potent inducer of chronic persistent infections, which lead (if untreated) to fibrosis. There are two key points concerning treatment of these viruses: while infection with HBV, but not HCV, can be prevented by vaccination, chronic HCV, but not HBV, infection can be successfully eliminated by treatment with direct-acting antiviral drugs. HCV infection induces release of type I (IFN-α/β) and type III (IFNλ) interferons, which increase expression of interferon-stimulated genes (ISGs), leading to an antiviral profile in the liver. By contrast, HBV infection does not induce production of interferons; hence, it results in impaired induction of ISG expression [120]. The outcome of HBV infection is determined by the adaptive immune response, represented by HBV-specific antibody-producing B cells, multi-specific polyclonal CD8+ cytotoxic T cells, and activated CD4+ T cells [121].

HBV induces inflammatory cytokine production by monocytes via TLR2/MyD88/NF-κB signaling but inhibits their IFN-α/β responsiveness and, consequently, effector functions mediated by ISGs; this suggests that, in contrast to HCV, HBV escapes surveillance by the innate immune system [120, 122]. Investigations into the role of monocytes and their contribution to the fate of viral liver infections are performed mainly in circulating monocytes due to the scarcity of HBV- or HCV-infected primary liver tissues and the lack of fully immunocompetent HBV/HCV murine models. Neither the abundance of different monocyte populations nor the function of monocytes in the peripheral blood of chronic HBV patients are altered, nor is their ability to induce T-cell cytokine production and proliferation after TLR stimulation [123, 124]. However, the frequency of intermediate CD14++CD16+ and non-classical CD14++CD16++ monocytes in immune-active patients is high and correlates with increased alanine transaminase (ALT) levels and liver histological activity index (HAI) scores, which may indicate a possible role for these cells in liver inflammation and fibrosis during chronic infection. More specifically, intermediate CD14++CD16+ and non-classical CD14++CD16++ monocytes in patients with immune-active hepatitis show increased expression of HLA-DR and inflammatory cytokines and have a greater capacity to induce expansion of the Th17 cell population [125]. Monocyte-derived macrophages and KCs in the liver have the potential to further accelerate the pro-inflammatory process; indeed, monocyte-derived macrophages and KCs interact with soluble factors such as hepatitis B surface antigen (HBsAg), resulting in cell activation and cytokine production, including pro-inflammatory cytokines [126]. Moreover, intrahepatic (pro-inflammatory) CD14+HLA-DRhiCD206+ myeloid cells have been linked to HBV-induced liver inflammation and subsequent fibrosis [127, 128]. However, HBsAg counteracts excessive immune activation by monocytes. Furthermore, *in vitro* analysis reveals that HBsAg suppresses pro-inflammatory cytokine production by LPS-stimulated monocytes [129]. HBV particles impair the allostimulatory capacity of monocyte-derived DCs, thereby reducing their potential to stimulate autologous T cells against a recall antigen and suppressing T helper cell type 1 responses [130]. HBeAg, another...
soluble virus factor, reduces production of TNF and IL-6 by peripheral mononuclear cells after TLR2-challenge [131].

As mentioned previously, HCV infection follows different mechanisms to escape from the immune system. Besides the activation of ISGs during HCV infection, classical monocytes from healthy donors, cultured with HCV-infected hepatoma cells or HCV alone, expressed pro- as well as anti-inflammatory cytokines and showed characteristic surface marker expression of alternatively activated macrophages, including CD206, which was also detected on monocytes from HCV-infected patients. [132]. Elevated hepatic macrophage numbers are characteristic for an HCV infection, which is associated with high levels of pro- and anti-inflammatory cytokines [133]. This explains the dual responses: hepatitis and apoptosis of infected hepatocytes caused by inflammatory cytokines as well as viral persistence due to deactivation of TLR3-mediated antiviral activities like interferon release or TRAIL expression by HCV [134]. Moreover, monocytes from chronically infected HCV patients showed an increased expression of programmed death (PD)-1 which correlated with an impaired IL-12 secretion [135].

Furthermore, during chronic HCV or HBV infection, Kupffer cells produce immunomodulatory mediators that suppress antiviral T-cell responses, such as IL-10, TGFβ, galectin-9, PD-L1, and PD-L2 [136]. Therefore, HCV infection induces an immune response, which favors a persistent of HCV and chronic course of disease.

Nevertheless, conducting functional in vivo studies to investigate early innate immune responses against HBV and HCV are challenging due to a lack of immunocompetent mouse models; therefore, lymphocytic choriomeningitis virus (LCMV), which establishes a persistent liver infection in mice, is used as a comparable murine model [137]. LCMV infection induces massive and early recruitment of inflammatory monocytes to the liver and increases liver-specific expression of mRNA encoding pro-inflammatory cytokines. However, compared with those recruited after conventional LPS challenge, LCMV-recruited monocytes are impaired in terms of their phagocytic capacity, and gene expression levels of TNF, IL-6, IL-10, CCL2, IP-10, and CCL5 are similar to those of KCs, which retain their phagocytic capacity after 24 h. The higher proportion of inflammatory monocytes compared with KCs during the early phase of infection suggests that inflammatory monocytes contribute to the intrahepatic inflammatory response, at least in the LCMV infection model [138]. LCMV also counteracts induction of neutralizing humoral immunity. Ly6C+ monocytes interact with LCMV-specific B cells in draining lymph nodes, thereby suppressing antiviral responses and reducing survival via production of NO [139]. During LCMV infection, the ability of inflammatory monocyte-primed CD8 T cells to efficiently produce inflammatory cytokines and granzyme B is reduced, suggesting that monocytes hamper the effector function of CD8 T cells [140].

In summary, several studies have shown that monocytes are affected by viral hepatitis and have a potential role in supporting immunopathology in the liver, especially in HBV-infected individuals; however, at the same time, viral infection may suppress or counteract monocyte activation. Further studies are needed to elucidate the mechanisms that affect the balance between monocyte suppression and activation in viral hepatitis and to identify new intervention points of treatment.

Conclusion

Adequate and regulated immune reactions are necessary to fight infections and to prevent immunopathology. Hepatic infections are particularly challenging because the liver needs to retain its immunotolerance profile with respect to harmless (but abundant) antigens such as nutrients from the intestinal system. Monocytes are part of innate immune response against pathogens that cause hepatic diseases. Recent findings show that rather than being categorized into only three groups, monocytes should be described as a population of highly diverse cells that have strong adaptive potential and exceptional plasticity with respect to combating injury and disease. Nevertheless, for many diseases, the CCR2/CCL2 axis plays a crucial role in recruiting monocytes to the site of injury. The described hepatic infections have one thing in common: an imbalance in the responses of monocytes, which has a crucial impact on disease course. As some infectious agents such as Leishmania parasites or DENV target monocytes directly, the diseases activate monocytes, which target invading parasites or infected cells via three major mechanisms: phagocytosis, antigen presentation to T cells, and cytokine expression. However, insufficient control of monocyte activation leads to immunopathology, as described for amebiasis and leishmaniasis, whereas suppression of monocytes triggers development of fibrosis (as in schistosomiasis and hepatitis B and C).

Directly targeting the function of monocytes to reduce immunopathology and cure diseases remains challenging [136]; however, a better understanding of the interaction between monocytes and the complex hepatic system is expected to identify new points of intervention and new treatments for hepatic diseases.

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Declarations

Competing interests The authors declare no competing interests.
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