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**Emerging roles of myeloid derived suppressor cells in hepatic inflammation and fibrosis**

Hammerich L *et al.* MDSC in liver disease

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**Abstract**

Myeloid derived suppressor cells (MDSC) are a heterogeneous population of immune cells that are potent suppressors of immune responses. MDSC emerge in various compartments in the body, such as blood, bone marrow or spleen, especially in conditions of cancer, infections or inflammation. MDSC usually express CD11b, CD33 and low levels of human leukocyte antigen-DR in humans or CD11b and Gr1 (Ly6C/G) in mice, and they can be further divided into granulocytic or monocytic MDSC. The liver is an important organ for MDSC induction and accumulation in hepatic as well as extrahepatic diseases. Different hepatic cells, especially hepatic stellate cells, as well as liver-derived soluble factors, especially hepatocyte growth factor and acute phase proteins (SAA, KC), can promote the differentiation of MDSC from myeloid cells. Importantly, hepatic myeloid cells like neutrophils, monocytes and macrophages fulfill essential roles in acute and chronic liver diseases. Recent data from patients with liver diseases and animal models linked MDSC to the pathogenesis of hepatic inflammation, fibrosis and hepatocellular carcinoma (HCC). In settings of acute hepatitis, MDSC can limit immunogenic T cell responses and subsequent tissue injury. In patients with chronic hepatitis C, MDSC increase and may favor viral persistence. Animal models of chronic liver injury, however, have not yet conclusively clarified the involvement of MDSC for hepatic fibrosis. In human HCC and mouse models of liver cancer, MDSC are induced in the tumor environment and suppress anti-tumoral immune responses. Thus, the liver is a primary site of MDSC *in vivo*, and modulating MDSC functionality might represent a promising novel therapeutic target for liver diseases.

**Key words:** Myeloid derived suppressor cells; Interleukin-10; Treg; Hepatitis C virus; Liver cirrhosis; Macrophage

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**Core tip:** Myeloid derived suppressor cells (MDSC) are a heterogeneous population of immune-suppressive cells with important roles during inflammation, infection and cancer. The liver is a primary site for MDSC induction and accumulation, and recent studies linked these cells to the pathogenesis of hepatic inflammation, fibrosis and hepatocellular carcinoma. MDSC can limit tissue injury during acute hepatitis, while they may favor viral persistence in chronic hepatitis. MDSC are also induced during development of liver cancer and suppress anti-tumoral immunity, but their involvement in hepatic fibrosis is less clear. Thus, modulating MDSC functionality might represent a promising novel therapeutic target for liver diseases.

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**INTRODUCTION**

Myeloid-derived suppressor cells (MDSC) are a heterogeneous cell population of myeloid origin originally described in tumor-bearing hosts[1] that are also induced under various inflammatory conditions - including sepsis[2], hepatitis[3,4] and viral infections[5-7]. MDSC regulate immune responses by potently suppressing T cell function[8]; although these T cell suppressive activities have been functionally linked to tumor progression or evasion from immune responses, the exact roles of MDSC appears to be context-dependent and vary between infectious, autoimmune or malignant diseases. MDSC are usually identified as CD11b+ CD33+ HLA-DRlow cells in humans and CD11b+ Gr1+ cells in mice[9]. However, a specific marker for MDSC has not been described so far, which can make identification of these cells difficult as all those surface molecules are shared with other myeloid cell types like neutrophils, monocytes or myeloid dendritic cells. Therefore, the most reliable feature to distinguish MDSC from other myeloid cells seems to be their suppressive function.

MDSC consist of at least two major subpopulations that are termed monocytic MDSC (mMDSC) and granulocytic MDSC (gMDSC) according to their side scatter (SSC) profile and Gr1 (Ly6C/G) expression in mice[10]. Whereas murine mMDSC have a low SSC profile and are Ly6Chi Ly6G-, gMDSC are Ly6Clo Ly6Ghi and show a higher SSC profile. In humans, CD14 and CD15 have been suggested as markers for mMDSC and gMDSC, respectively, but further investigation is needed to verify this hypothesis[11]. The two subsets seem to differ in their suppressive capacity and functional mechanism(s) depending on the disease studied.

As MDSC are heterogeneous myeloid cells with immune suppressive functions, several mechanisms of T cell suppression have been described. These mechanisms of T cell suppression include L-arginine depletion by the enzymes arginase 1 (Arg1) or inducible nitric oxide synthase (iNOS) and generation of reactive oxygen species (ROS)[8,10,12]. Furthermore, MDSC have also been shown to secrete anti-inflammatory cytokines like IL-10[13]. Again, the suppressive mechanisms used by the different subsets as well as the requirement of cell-cell-contacts vs. secretion of soluble factors seem to be highly dependent on the underlying pathology (Table 1). A recent study on the development of murine MDSC suggested that the two subsets depend on the expression of distinct anti-apoptotic proteins and that T cell suppressive functions are restricted to the mMDSC subset[14].

**THE LIVER AS A SITE OF MDSC ACCUMULATION AND INDUCTION**

The liver has been shown to be a site of MDSC accumulation, and this seems to apply to hepatic and also to extrahepatic diseases. Different hepatic cell types as well as liver-derived soluble factors have been implicated in the recruitment and differentiation of MDSC under various conditions (Figure 1). In tumor-bearing mice with various types of cancer – including breast, lung and skin cancer – MDSC numbers increased in the liver irrespective of whether the mice had tumor manifestation in the liver, namely hepatic metastasis, or not[15]. Furthermore, adoptively transferred MDSC homed to livers and spleens of tumor-bearing mice in a comparable fashion. Ilkovitch *et al*[15] could show that this increase in hepatic MDSC is at least in part due to elevated levels of GM-CSF, a hematopoietic growth factor produced by many different types of tumors and associated with splenic accumulation of MDSC.

Additionally, hepatic stellate cells (HSC), a cell type associated with various immune-modulatory functions[16], have been shown to induce MDSC from myeloid cells in mice and men. Primary human HSC were able to induce differentiation of MDSC from PBMC *in vitro*[17]. This induction was dependent on direct cell-cell contacts as well as on the expression of CD44 by HSC and led to generation of CD14+ HLA-DRlo cells able to suppress T cell responses in an arginase 1-dependent manner. Similarly, murine hepatic stellate cells were proven to induce CD11b+Gr1+ MDSC from bone marrow-derived cells[18,19]. However, this induction seems to be mediated by soluble factors rather than cell-cell contact. Chou *et al*[18] implicated a critical role for IFNγ signaling in HSC, and an additional study from the same group showed that MDSC induction was mediated by complement component C3 released by HSC[19]. In addition, both studies demonstrated that HSC could also induce MDSC *in vivo* in the context of islet cell transplantation and therefore contribute to allograft survival.

Furthermore, liver-derived soluble factors can also promote the generation of MDSC (Figure 1). Human mesenchymal stromal cells and an osteosarcoma cell line are able to induce the expansion of CD11b+ CD33+ CD14- MDSC from peripheral blood leukocytes *in vitro*, an effect that is mediated by hepatocyte growth factor (HGF) and its receptor c-Met[20]. Since the liver usually harbors high levels of HGF this might be an explanation for the high numbers of MDSC present in the liver even under steady state conditions. Indeed, inhibition of the HGF/c-Met pathway in mice led to a significant reduction in hepatic but not splenic MDSC[20]. In the context of polymicrobial sepsis in mice hepatic acute-phase proteins play a critical role for controlling the inflammatory reaction to infection. Both serum amyloid A (SAA) and the chemokine CXCL1/KC work synergistically to mobilize MDSC from the bone marrow and induce their accumulation in the spleen[2]. Mice lacking the production of acute phase proteins due to the deletion of the IL-6 cytokine family receptor gp130 in hepatocytes showed less accumulation of MDSC and increased mortality during sepsis, which could be reversed by adoptive transfer of MDSC or administration of recombinant SAA and KC[2]. Consistently, the ectopic expression of IL-6 in the liver could induce accumulation of MDSC in liver and spleen, which protected mice from CD8+ T cell-mediated liver injury[21].

Another factor that should be considered for the accumulation of MDSC in the liver is activation of inflammasomes, proteolytic complexes activated by pattern recognition receptors (PRR) and resulting in the production of IL-1β and IL-18. In murine cancer models activation of the Nlrp3 inflammasome has been associated with the accumulation of MDSC and suppression of anti-tumor immune responses[22,23]. This might also apply to liver diseases as inflammasome activation is important in a wide range of conditions[24,25]. Chronic human liver diseases are often associated with changes in the intestinal microbiome with the resulting inflammation leading to disruption and enhanced permeability of the intestinal epithelial barrier[26,27]. This enables the translocation of microbial products, which can travel to the liver *via* the portal vein and activate the inflammasome complex through PRRs. So far, this process has mainly been described for liver macrophages[28], but considering what has been observed for tumor-associated MDSC inflammasome activation might also induce accumulation of hepatic MDSC.

**MDSC IN THE REGULATION OF HUMAN LIVER DISEASES**

While the above mentioned data demonstrated that the liver is an important site of MDSC induction for extrahepatic infections and cancer, more recent data implied hepatic MDSC as essential regulators of liver diseases as well. Several studies have concordantly reported that patients with hepatocellular carcinoma (HCC) or chronic hepatitis C virus (HCV) infection show increased frequencies of MDSC in the peripheral blood[6,7,29-32]. Human MDSC in HCC patients are mainly CD14+ HLA-DR-/low and able to inhibit T cell proliferation in an arginase dependent manner[29]. Furthermore, these cells induce a regulatory phenotype in CD4+ T cells and inhibit natural killer (NK) cell function *in vitro*[29,33]. Likewise, MDSC in the blood of patients with chronic HCV were shown to be CD11b+ HLA-DRlow CD14+ CD33+ and suppress T cells using arginase[6]. In addition, ROS production might contribute to T cell inhibition by MDSC, and HCV-infected hepatocytes were found to promote MDSC differentiation from PBMC[7]. This might represent a mechanism of HCV-mediated immune suppression that leads to persistent infection.

**ROLE OF MDSC FOR HEPATOCELLULAR CARCINOMA**

Several studies have addressed the function of MDSC in liver cancer by investigating murine models of HCC. Mice bearing liver tumors show increased numbers of MDSC in liver, spleen and bone marrow[34-37]. Remarkably, the timing of MDSC accumulation seems to be highly dependent on the tumor model studied. Mice with diethylnitrosamine (DEN) or transgenic myc-overexpression induced liver tumors, in which primary liver cancer develops slowly in the “normal” hepatic microenvironment, showed increased MDSC numbers only during late stages of the disease, while mice with orthotopic or subcutaneous tumors displayed increased MDSC numbers early on[34]. In addition, MDSC from mice with transplantable tumors showed higher suppressive capacity than MDSC from mice with DEN-induced HCC. Several studies showed that treatment with the multi-kinase inhibitor sorafenib[34,35] or an agonistic anti-CD137 antibody[37] decreased frequency of MDSC in mice bearing HCC, thereby contributing to anti-tumoral immunity.

Several soluble factors have been implicated in the recruitment of MDSC during HCC development. Tumor derived GM-CSF and KC mediated the accumulation of MDSC during hepatocarcinogenesis, and neutralization of these molecules reduced hepatic MDSC numbers[34]. Interleukin-17 (IL-17) produced by gamma/delta T cells (γδ T cells) also indirectly mediated MDSC accumulation[38]. Ma and coworkers showed that γδ T cell-derived IL-17 induced secretion of CXCL5 by tumor cells, which then recruited MDSC *via* engagement of CXCR2. Moreover, IL-17 also acted on the MDSC directly by enhancing their suppressive capacity and MDSC enhanced the production of IL-17 by γδ T cells through release of IL-23 and IL-1β[38]. Similarly, γδ T cell-derived IL-17 has also been shown to recruit MDSC to the liver in HBV-transgenic mice, where they induce CD8 T cell exhaustion and HBV tolerance[5].

In DEN-induced liver carcinogenesis IL-18 is also involved in recruitment of MDSC to the liver. Li *et al*[39] demonstrated recently that TLR2-deficient mice develop more aggressive HCC than wt mice associated with increased numbers of MDSC in the liver. This was mediated by IL-18 produced by hepatocytes and could be reversed through silencing of IL-18.

Interestingly, MDSC have also been associated with the development of liver metastasis. Mice with different types of intra-abdominal tumors showed a significant accumulation of MDSC in the liver that were able to potently suppress cytotoxic T cells and induce regulatory T cells[40]. Hepatic MDSC also differed from splenic MDSC in these models, expressing higher levels of immune-modulatory cytokines and being primarily of a monocytic phenotype. Similarly to HCC development, hepatic accumulation of MDSC was mediated by tumor-derived KC. This suggests that MDSC promote the development of liver metastases and might provide an explanation why human intra-abdominal cancers metastasize preferentially to the liver[41].

**ROLE OF MDSC IN MOUSE MODELS OF LIVER INFLAMMATION AND FIBROSIS**

The accumulation of neutrophils, monocytes and macrophages is a hallmark of acute and chronic liver inflammation. For instance, hepatic neutrophils are associated with drug-induced liver injury, alcoholic hepatitis or ischemia-reperfusion injury[42]. Hepatic macrophages are a remarkably heterogeneous population comprising myeloid cells with different origins (*e.g.*, resident Kupffer cells vs infiltrating monocyte-derived macrophages) and distinct properties[43]. Some of these neutrophils and macrophages have a clear immunosuppressive phenotype, prompting research on MDSC in acute and chronic liver injury.

Recently, MDSC have been studied in the context of acute liver inflammation and are usually associated with protective functions in this setting. We and others could show that MDSC accumulate in the liver during Concanavalin A (ConA)-, D-galactosamine (D-gal) - and picryl chloride-induced hepatitis[3,4,44-47] and protect the liver from excessive damage. However, there seems to be controversy about which subsets are preferentially involved and which suppressive mechanisms they use. Two independent studies showed that administration of cannabidiol[4] or IL-25[3] could increase the number of hepatic CD11b+ Gr1+ cells that ameliorated organ damage upon immune-mediated hepatitis. In this setting, the ratio of gMDSC to mMDSC was about 2:1, and T cell responses were inhibited in an arginase-dependent manner with mMDSC being more suppressive than gMDSC[4]. Consistently, we have shown that inhibiting the suppressive capacity specifically in the mMDSC subset led to severely aggravated hepatitis upon ConA-challenge[44]. Similar observations were also made by another group studying the role of FTY720, a sphingosine-1-phosphate receptor agonist, in recruitment of MDSC to the liver[46,47]. However, suppressive function of these cells was dependent on iNOS and NO production rather than arginine depletion by Arg1. Furthermore, these studies also provided some insight into how MDSC are recruited to the liver. Similarly to what has been observed in liver cancer, MDSC accumulation was mediated *via* CXCR2[46,47]. In contrast to the aforementioned studies, Zhu and colleagues showed that, although both MDSC subtypes were recruited, only mMDSC were able to suppress T cell responses and limit liver damage in ConA-mediated hepatitis[45]. This was also observed in acutely inflamed livers of Tgfβ1-/- mice[48], where both subtypes of MDSC accumulated but only mMDSC were capable of suppressing T cells utilizing iNOS.

Overall, the liver provides a unique tolerogenic microenvironment, and several antigen-presenting cells contribute to the suppression of immunogenic T cell responses in the liver[49]. It has become increasingly clear that immune tolerance can also occur during chronic liver diseases. On the one hand, such tolerogenic mechanisms may limit intrahepatic immune responses and subsequent tissue injury, but on the other hand, immune tolerance may restrain eradication of pathogens and favor chronic infections[50]. Only limited data is available on the involvement of MDSC in chronic liver injury and the development of liver fibrosis. A recent study by Suh *et al*[13] indicates that bone marrow-derived MDSC can ameliorate hepatofibrogenesis through the production of IL-10, which downregulates pro-fibrotic functions of activated HSC. Interestingly, IL-10 production was induced upon contact with activated HSC *in vitro*, suggesting a mechanism for the beneficial effects observed in patients and mice with hepatic fibrosis treated with infusion of bone marrow cells[51]. On the contrary, liver fibrosis development upon chronic injury was not affected in a mouse model of transgenic overexpression of the transcription factor crem-alpha, which impairs the functionality of hepatic mMDSC[44]. Thus, more data are needed to define the possible role of MDSC in chronic inflammatory settings in the liver, and their involvement may likely vary depending on the etiology of the underlying disease, e.g. autoimmunity, chronic viral hepatitis or metabolic injury.

**MDSC AS THERAPEUTIC TARGETS FOR THE TREATMENT OF LIVER DISEASES**

Given that MDSC are mainly associated with pathogenic functions in human chronic liver diseases such as chronic viral infections or liver cancer development, depletion of these cells and/or inhibition of their development may hold high potential in the treatment of such diseases. It has been shown that MDSC can be differentiated from murine bone-marrow cells and human PBMC *in vitro* in the presence of GM-CSF and IL-6[52-54]. Thus, these cytokines might be therapeutically targeted to avoid development of MDSC *in vivo*, but due to the various other functions of these cytokines, systemic inhibition might not be feasible and methods of local inhibition should be explored. In tumor bearing mice depletion of MDSC using a Gr-1 specific antibody has proven to help with eradication of tumors and prevention of recurrence[55,56]. However, a more recent study reported that this antibody failed to completely eliminate hepatic MDSC[57] challenging the feasibility of this approach for liver disease therapy. Since MDSC are considered immature cells, influencing the differentiation of these cells into other myeloid cells that promote rather than inhibit immune responses could be a different therapeutic approach. Retinoic acid and vitamin D3 have both been implicated in the differentiation of MDSC to dendritic cells *in vitro* and administrations of these agents to tumor-bearing mice or cancer patients resulted in the significant improvement of anti-tumor immune responses[58-61].

In murine models of acute liver inflammation MDSC have been associated with protective rather than pathogenic functions. Therefore, it might be helpful to enhance hepatic MDSC numbers for the treatment of patients with acute inflammation or autoimmunity in the liver. The previously mentioned induction of MDSC from PBMC using GM-CSF and IL-6 would allow for the generation and expansion of autologous MDSC that can then be retransferred to the patient. The fact that adoptively transferred MDSC preferentially home to the liver[15] acts in favor of this approach allowing directed delivery of MDSC to the site of inflammation. However, migration of MDSC and “off-target” T cell suppression cannot be ruled out and should be considered in this setting.

Taken together, MDSC represent promising therapeutic targets in the treatment of liver diseases, but more extensive research is needed before these approaches can be used in clinical settings.

**REFERENCES**

1 **Talmadge JE**, Gabrilovich DI. History of myeloid-derived suppressor cells. *Nat Rev Cancer* 2013; **13**: 739-752 [PMID: 24060865 DOI: 10.1038/nrc3581]

2 **Sander LE**, Sackett SD, Dierssen U, Beraza N, Linke RP, Müller M, Blander JM, Tacke F, Trautwein C. Hepatic acute-phase proteins control innate immune responses during infection by promoting myeloid-derived suppressor cell function. *J Exp Med* 2010; **207**: 1453-1464 [PMID: 20530204 DOI: 10.1084/jem.20091474]

3 **Sarra M**, Cupi ML, Bernardini R, Ronchetti G, Monteleone I, Ranalli M, Franzè E, Rizzo A, Colantoni A, Caprioli F, Maggioni M, Gambacurta A, Mattei M, Macdonald TT, Pallone F, Monteleone G. IL-25 prevents and cures fulminant hepatitis in mice through a myeloid-derived suppressor cell-dependent mechanism. *Hepatology* 2013; **58**: 1436-1450 [PMID: 23564603 DOI: 10.1002/hep.26446]

4 **Hegde VL**, Nagarkatti PS, Nagarkatti M. Role of myeloid-derived suppressor cells in amelioration of experimental autoimmune hepatitis following activation of TRPV1 receptors by cannabidiol. *PLoS One* 2011; **6**: e18281 [PMID: 21483776 DOI: 10.1371/journal.pone.0018281]

5 **Kong X**, Sun R, Chen Y, Wei H, Tian Z. γδT cells drive myeloid-derived suppressor cell-mediated CD8+ T cell exhaustion in hepatitis B virus-induced immunotolerance. *J Immunol* 2014; **193**: 1645-1653 [PMID: 25015833 DOI: 10.4049/jimmunol.1303432]

6 **Cai W**, Qin A, Guo P, Yan D, Hu F, Yang Q, Xu M, Fu Y, Zhou J, Tang X. Clinical significance and functional studies of myeloid-derived suppressor cells in chronic hepatitis C patients. *J Clin Immunol* 2013; **33**: 798-808 [PMID: 23354838 DOI: 10.1007/s10875-012-9861-2]

7 **Tacke RS**, Lee HC, Goh C, Courtney J, Polyak SJ, Rosen HR, Hahn YS. Myeloid suppressor cells induced by hepatitis C virus suppress T-cell responses through the production of reactive oxygen species. *Hepatology* 2012; **55**: 343-353 [PMID: 21953144 DOI: 10.1002/hep.24700]

8 **Youn JI**, Gabrilovich DI. The biology of myeloid-derived suppressor cells: the blessing and the curse of morphological and functional heterogeneity. *Eur J Immunol* 2010; **40**: 2969-2975 [PMID: 21061430 DOI: 10.1002/eji.201040895]

9 **Poschke I**, Kiessling R. On the armament and appearances of human myeloid-derived suppressor cells. *Clin Immunol* 2012; **144**: 250-268 [PMID: 22858650 DOI: 10.1016/j.clim.2012.06.003]

10 **Movahedi K**, Guilliams M, Van den Bossche J, Van den Bergh R, Gysemans C, Beschin A, De Baetselier P, Van Ginderachter JA. Identification of discrete tumor-induced myeloid-derived suppressor cell subpopulations with distinct T cell-suppressive activity. *Blood* 2008; **111**: 4233-4244 [PMID: 18272812 DOI: 10.1182/blood-2007-07-099226]

11 **Greten TF**, Manns MP, Korangy F. Myeloid derived suppressor cells in human diseases. *Int Immunopharmacol* 2011; **11**: 802-807 [PMID: 21237299 DOI: 10.1016/j.intimp.2011.01.003]

12 **Youn JI**, Nagaraj S, Collazo M, Gabrilovich DI. Subsets of myeloid-derived suppressor cells in tumor-bearing mice. *J Immunol* 2008; **181**: 5791-5802 [PMID: 18832739]

13 **Suh YG**, Kim JK, Byun JS, Yi HS, Lee YS, Eun HS, Kim SY, Han KH, Lee KS, Duester G, Friedman SL, Jeong WI. CD11b(+) Gr1(+) bone marrow cells ameliorate liver fibrosis by producing interleukin-10 in mice. *Hepatology* 2012; **56**: 1902-1912 [PMID: 22544759 DOI: 10.1002/hep.25817]

14 **Haverkamp JM**, Smith AM, Weinlich R, Dillon CP, Qualls JE, Neale G, Koss B, Kim Y, Bronte V, Herold MJ, Green DR, Opferman JT, Murray PJ. Myeloid-derived suppressor activity is mediated by monocytic lineages maintained by continuous inhibition of extrinsic and intrinsic death pathways. *Immunity* 2014; **41**: 947-959 [PMID: 25500368 DOI: 10.1016/j.immuni.2014.10.020]

15 **Ilkovitch D**, Lopez DM. The liver is a site for tumor-induced myeloid-derived suppressor cell accumulation and immunosuppression. *Cancer Res* 2009; **69**: 5514-5521 [PMID: 19549903 DOI: 10.1158/0008-5472.CAN-08-4625]

16 **Weiskirchen R**, Tacke F. Cellular and molecular functions of hepatic stellate cells in inflammatory responses and liver immunology. *Hepatobiliary Surg Nutr* 2014; **3**: 344-363 [PMID: 25568859]

17 **Höchst B**, Schildberg FA, Sauerborn P, Gäbel YA, Gevensleben H, Goltz D, Heukamp LC, Türler A, Ballmaier M, Gieseke F, Müller I, Kalff J, Kurts C, Knolle PA, Diehl L. Activated human hepatic stellate cells induce myeloid derived suppressor cells from peripheral blood monocytes in a CD44-dependent fashion. *J Hepatol* 2013; **59**: 528-535 [PMID: 23665041 DOI: 10.1016/j.jhep.2013.04.033]

18 **Chou HS**, Hsieh CC, Yang HR, Wang L, Arakawa Y, Brown K, Wu Q, Lin F, Peters M, Fung JJ, Lu L, Qian S. Hepatic stellate cells regulate immune response by way of induction of myeloid suppressor cells in mice. *Hepatology* 2011; **53**: 1007-1019 [PMID: 21374665 DOI: 10.1002/hep.24162]

19 **Hsieh CC**, Chou HS, Yang HR, Lin F, Bhatt S, Qin J, Wang L, Fung JJ, Qian S, Lu L. The role of complement component 3 (C3) in differentiation of myeloid-derived suppressor cells. *Blood* 2013; **121**: 1760-1768 [PMID: 23299310 DOI: 10.1182/blood-2012-06-440214]

20 **Yen BL**, Yen ML, Hsu PJ, Liu KJ, Wang CJ, Bai CH, Sytwu HK. Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-met and STAT3. *Stem Cell Reports* 2013; **1**: 139-151 [PMID: 24052949 DOI: 10.1016/j.stemcr.2013.06.006]

21 **Cheng L**, Wang J, Li X, Xing Q, Du P, Su L, Wang S. Interleukin-6 induces Gr-1+CD11b+ myeloid cells to suppress CD8+ T cell-mediated liver injury in mice. *PLoS One* 2011; **6**: e17631 [PMID: 21394214 DOI: 10.1371/journal.pone.0017631]

22 **van Deventer HW**, Burgents JE, Wu QP, Woodford RM, Brickey WJ, Allen IC, McElvania-Tekippe E, Serody JS, Ting JP. The inflammasome component NLRP3 impairs antitumor vaccine by enhancing the accumulation of tumor-associated myeloid-derived suppressor cells. *Cancer Res* 2010; **70**: 10161-10169 [PMID: 21159638 DOI: 10.1158/0008-5472.CAN-10-1921]

23 **Bruchard M**, Mignot G, Derangère V, Chalmin F, Chevriaux A, Végran F, Boireau W, Simon B, Ryffel B, Connat JL, Kanellopoulos J, Martin F, Rébé C, Apetoh L, Ghiringhelli F. Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. *Nat Med* 2013; **19**: 57-64 [PMID: 23202296 DOI: 10.1038/nm.2999]

24 **Mehal WZ**. The inflammasome in liver injury and non-alcoholic fatty liver disease. *Dig Dis* 2014; **32**: 507-515 [PMID: 25034283 DOI: 10.1159/000360495]

25 **Bieghs V**, Trautwein C. Innate immune signaling and gut-liver interactions in non-alcoholic fatty liver disease. *Hepatobiliary Surg Nutr* 2014; **3**: 377-385 [PMID: 25568861 DOI: 10.3978/j.issn.2304-3881.2014.12.04]

26 **Schnabl B**, Brenner DA. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology* 2014; **146**: 1513-1524 [PMID: 24440671 DOI: 10.1053/j.gastro.2014.01.020]

27 **Qin N**, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Chen Y, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014; **513**: 59-64 [PMID: 25079328 DOI: 10.1038/nature13568]

28 **Szabo G**, Csak T. Inflammasomes in liver diseases. *J Hepatol* 2012; **57**: 642-654 [PMID: 22634126 DOI: 10.1016/j.jhep.2012.03.035]

29 **Hoechst B**, Ormandy LA, Ballmaier M, Lehner F, Krüger C, Manns MP, Greten TF, Korangy F. A new population of myeloid-derived suppressor cells in hepatocellular carcinoma patients induces CD4(+)CD25(+)Foxp3(+) T cells. *Gastroenterology* 2008; **135**: 234-243 [PMID: 18485901 DOI: 10.1053/j.gastro.2008.03.020]

30 **Kalathil S**, Lugade AA, Miller A, Iyer R, Thanavala Y. Higher frequencies of GARP(+)CTLA-4(+)Foxp3(+) T regulatory cells and myeloid-derived suppressor cells in hepatocellular carcinoma patients are associated with impaired T-cell functionality. *Cancer Res* 2013; **73**: 2435-2444 [PMID: 23423978 DOI: 10.1158/0008-5472.CAN-12-3381]

31 **Mundy-Bosse BL**, Young GS, Bauer T, Binkley E, Bloomston M, Bill MA, Bekaii-Saab T, Carson WE, Lesinski GB. Distinct myeloid suppressor cell subsets correlate with plasma IL-6 and IL-10 and reduced interferon-alpha signaling in CD4⁺ T cells from patients with GI malignancy. *Cancer Immunol Immunother* 2011; **60**: 1269-1279 [PMID: 21604071 DOI: 10.1007/s00262-011-1029-z]

32 **Liu Y**, She LH, Wang XY, Zhang GL, Yan Y, Lin CS, Zhao ZX, Gao ZL. Expansion of myeloid-derived suppressor cells from peripheral blood decreases after 4-week antiviral treatment in patients with chronic hepatitis C. *Int J Clin Exp Med* 2014; **7**: 998-1004 [PMID: 24955173]

33 **Hoechst B**, Voigtlaender T, Ormandy L, Gamrekelashvili J, Zhao F, Wedemeyer H, Lehner F, Manns MP, Greten TF, Korangy F. Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. *Hepatology* 2009; **50**: 799-807 [PMID: 19551844 DOI: 10.1002/hep.23054]

34 **Kapanadze T**, Gamrekelashvili J, Ma C, Chan C, Zhao F, Hewitt S, Zender L, Kapoor V, Felsher DW, Manns MP, Korangy F, Greten TF. Regulation of accumulation and function of myeloid derived suppressor cells in different murine models of hepatocellular carcinoma. *J Hepatol* 2013; **59**: 1007-1013 [PMID: 23796475 DOI: 10.1016/j.jhep.2013.06.010]

35 **Cao M**, Xu Y, Youn JI, Cabrera R, Zhang X, Gabrilovich D, Nelson DR, Liu C. Kinase inhibitor Sorafenib modulates immunosuppressive cell populations in a murine liver cancer model. *Lab Invest* 2011; **91**: 598-608 [PMID: 21321535 DOI: 10.1038/labinvest.2010.205]

36 **Schneider C**, Teufel A, Yevsa T, Staib F, Hohmeyer A, Walenda G, Zimmermann HW, Vucur M, Huss S, Gassler N, Wasmuth HE, Lira SA, Zender L, Luedde T, Trautwein C, Tacke F. Adaptive immunity suppresses formation and progression of diethylnitrosamine-induced liver cancer. *Gut* 2012; **61**: 1733-1743 [PMID: 22267597 DOI: 10.1136/gutjnl-2011-301116]

37 **Gauttier V**, Judor JP, Le Guen V, Cany J, Ferry N, Conchon S. Agonistic anti-CD137 antibody treatment leads to antitumor response in mice with liver cancer. *Int J Cancer* 2014; **135**: 2857-2867 [PMID: 24789574 DOI: 10.1002/ijc.28943]

38 **Ma S**, Cheng Q, Cai Y, Gong H, Wu Y, Yu X, Shi L, Wu D, Dong C, Liu H. IL-17A produced by γδ T cells promotes tumor growth in hepatocellular carcinoma. *Cancer Res* 2014; **74**: 1969-1982 [PMID: 24525743 DOI: 10.1158/0008-5472.CAN-13-2534]

39 **Li S**, Sun R, Chen Y, Wei H, Tian Z. TLR2 Limits Development of Hepatocellular Carcinoma by Reducing IL18-Mediated Immunosuppression. *Cancer Res* 2015; **75**: 986-995 [PMID: 25600646 DOI: 10.1158/0008-5472.CAN-14-2371]

40 **Connolly MK**, Mallen-St Clair J, Bedrosian AS, Malhotra A, Vera V, Ibrahim J, Henning J, Pachter HL, Bar-Sagi D, Frey AB, Miller G. Distinct populations of metastases-enabling myeloid cells expand in the liver of mice harboring invasive and preinvasive intra-abdominal tumor. *J Leukoc Biol* 2010; **87**: 713-725 [PMID: 20042467 DOI: 10.1189/jlb.0909607]

41 **McMillan DC**, McArdle CS. Epidemiology of colorectal liver metastases. *Surg Oncol* 2007; **16**: 3-5 [PMID: 17493802 DOI: 10.1016/j.suronc.2007.04.008]

42 **Moles A**, Murphy L, Wilson CL, Chakraborty JB, Fox C, Park EJ, Mann J, Oakley F, Howarth R, Brain J, Masson S, Karin M, Seki E, Mann DA. A TLR2/S100A9/CXCL-2 signaling network is necessary for neutrophil recruitment in acute and chronic liver injury in the mouse. *J Hepatol* 2014; **60**: 782-791 [PMID: 24333183 DOI: 10.1016/j.jhep.2013.12.005]

43 **Tacke F**, Zimmermann HW. Macrophage heterogeneity in liver injury and fibrosis. *J Hepatol* 2014; **60**: 1090-1096 [PMID: 24412603 DOI: 10.1016/j.jhep.2013.12.025]

44 **Hammerich L**, Warzecha KT, Stefkova M, Bartneck M, Ohl K, Gassler N, Luedde T, Trautwein C, Tenbrock K, Tacke F. Cyclic adenosine monophosphate-responsive element modulator alpha overexpression impairs function of hepatic myeloid-derived suppressor cells and aggravates immune-mediated hepatitis in mice. *Hepatology* 2015; **61**: 990-1002 [PMID: 25330465 DOI: 10.1002/hep.27571]

45 **Zhu K**, Zhang N, Guo N, Yang J, Wang J, Yang C, Yang C, Zhu L, Xu C, Deng Q, Zhu R, Wang H, Chen X, Shi Y, Li Y, Leng Q. SSC(high)CD11b(high)Ly-6C(high)Ly-6G(low) myeloid cells curtail CD4 T cell response by inducible nitric oxide synthase in murine hepatitis. *Int J Biochem Cell Biol* 2014; **54**: 89-97 [PMID: 25035167 DOI: 10.1016/j.biocel.2014.07.005]

46 **Liu G**, Bi Y, Wang R, Yang H, Zhang Y, Wang X, Liu H, Lu Y, Zhang Z, Chen W, Chu Y, Yang R. Targeting S1P1 receptor protects against murine immunological hepatic injury through myeloid-derived suppressor cells. *J Immunol* 2014; **192**: 3068-3079 [PMID: 24567529 DOI: 10.4049/jimmunol.1301193]

47 **Zhang Y**, Bi Y, Yang H, Chen X, Liu H, Lu Y, Zhang Z, Liao J, Yang S, Chu Y, Yang R, Liu G. mTOR limits the recruitment of CD11b+Gr1+Ly6Chigh myeloid-derived suppressor cells in protecting against murine immunological hepatic injury. *J Leukoc Biol* 2014; **95**: 961-970 [PMID: 24569105 DOI: 10.1189/jlb.0913473]

48 **Cripps JG**, Wang J, Maria A, Blumenthal I, Gorham JD. Type 1 T helper cells induce the accumulation of myeloid-derived suppressor cells in the inflamed Tgfb1 knockout mouse liver. *Hepatology* 2010; **52**: 1350-1359 [PMID: 20803559 DOI: 10.1002/hep.23841]

49 **Thomson AW**, Knolle PA. Antigen-presenting cell function in the tolerogenic liver environment. *Nat Rev Immunol* 2010; **10**: 753-766 [PMID: 20972472 DOI: 10.1038/nri2858]

50 **Crispe IN**. Immune tolerance in liver disease. *Hepatology* 2014; **60**: 2109-2117 [PMID: 24913836 DOI: 10.1002/hep.27254]

51 **Thomas JA**, Pope C, Wojtacha D, Robson AJ, Gordon-Walker TT, Hartland S, Ramachandran P, Van Deemter M, Hume DA, Iredale JP, Forbes SJ. Macrophage therapy for murine liver fibrosis recruits host effector cells improving fibrosis, regeneration, and function. *Hepatology* 2011; **53**: 2003-2015 [PMID: 21433043 DOI: 10.1002/hep.24315]

52 **Lechner MG**, Liebertz DJ, Epstein AL. Characterization of cytokine-induced myeloid-derived suppressor cells from normal human peripheral blood mononuclear cells. *J Immunol* 2010; **185**: 2273-2284 [PMID: 20644162 DOI: 10.4049/jimmunol.1000901]

53 **Marigo I**, Bosio E, Solito S, Mesa C, Fernandez A, Dolcetti L, Ugel S, Sonda N, Bicciato S, Falisi E, Calabrese F, Basso G, Zanovello P, Cozzi E, Mandruzzato S, Bronte V. Tumor-induced tolerance and immune suppression depend on the C/EBPbeta transcription factor. *Immunity* 2010; **32**: 790-802 [PMID: 20605485 DOI: 10.1016/j.immuni.2010.05.010]

54 **Highfill SL**, Rodriguez PC, Zhou Q, Goetz CA, Koehn BH, Veenstra R, Taylor PA, Panoskaltsis-Mortari A, Serody JS, Munn DH, Tolar J, Ochoa AC, Blazar BR. Bone marrow myeloid-derived suppressor cells (MDSCs) inhibit graft-versus-host disease (GVHD) via an arginase-1-dependent mechanism that is up-regulated by interleukin-13. *Blood* 2010; **116**: 5738-5747 [PMID: 20807889 DOI: 10.1182/blood-2010-06-287839]

55 **Seung LP**, Rowley DA, Dubey P, Schreiber H. Synergy between T-cell immunity and inhibition of paracrine stimulation causes tumor rejection. *Proc Natl Acad Sci U S A* 1995; **92**: 6254-6258 [PMID: 7603979]

56 **Terabe M**, Matsui S, Park JM, Mamura M, Noben-Trauth N, Donaldson DD, Chen W, Wahl SM, Ledbetter S, Pratt B, Letterio JJ, Paul WE, Berzofsky JA. Transforming growth factor-beta production and myeloid cells are an effector mechanism through which CD1d-restricted T cells block cytotoxic T lymphocyte-mediated tumor immunosurveillance: abrogation prevents tumor recurrence. *J Exp Med* 2003; **198**: 1741-1752 [PMID: 14657224 DOI: 10.1084/jem.20022227]

57 **Ma C**, Kapanadze T, Gamrekelashvili J, Manns MP, Korangy F, Greten TF. Anti-Gr-1 antibody depletion fails to eliminate hepatic myeloid-derived suppressor cells in tumor-bearing mice. *J Leukoc Biol* 2012; **92**: 1199-1206 [PMID: 23077247 DOI: 10.1189/jlb.0212059]

58 **Young MR**, Ihm J, Lozano Y, Wright MA, Prechel MM. Treating tumor-bearing mice with vitamin D3 diminishes tumor-induced myelopoiesis and associated immunosuppression, and reduces tumor metastasis and recurrence. *Cancer Immunol Immunother* 1995; **41**: 37-45 [PMID: 7641218]

59 **Young MR**, Lathers DM. Myeloid progenitor cells mediate immune suppression in patients with head and neck cancers. *Int J Immunopharmacol* 1999; **21**: 241-252 [PMID: 10408632]

60 **Hengesbach LM**, Hoag KA. Physiological concentrations of retinoic acid favor myeloid dendritic cell development over granulocyte development in cultures of bone marrow cells from mice. *J Nutr* 2004; **134**: 2653-2659 [PMID: 15465762]

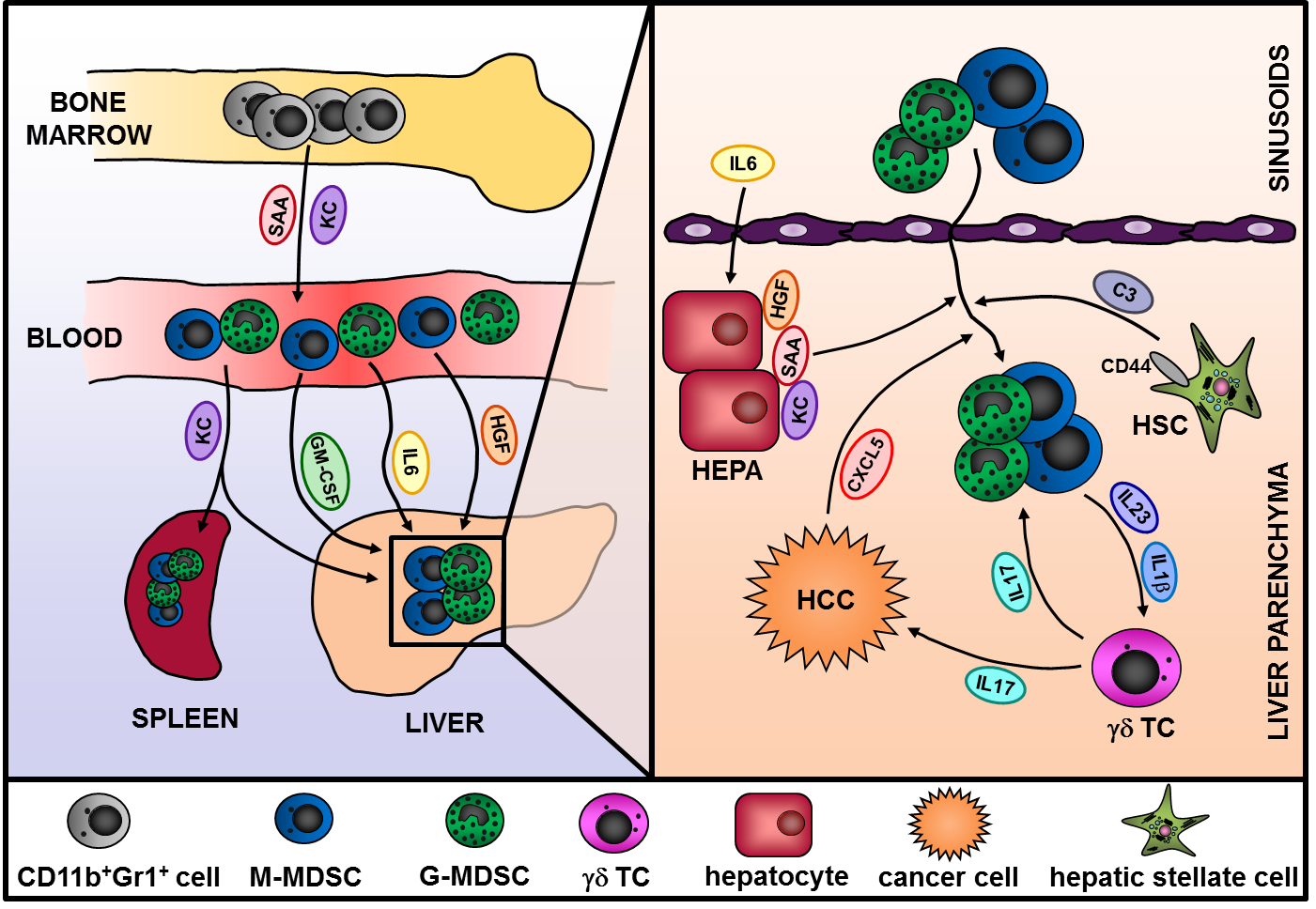
61 **Mirza N**, Fishman M, Fricke I, Dunn M, Neuger AM, Frost TJ, Lush RM, Antonia S, Gabrilovich DI. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. *Cancer Res* 2006; **66**: 9299-9307 [PMID: 16982775 DOI: 10.1158/0008-5472.CAN-06-1690]

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**Table 1 Functional role of myeloid derived suppressor cells in the regulation of human and murine liver diseases**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Species** | **Type of disease** | **Surface phenotype** | **Function of MDSC** | **mechanism** | **Ref.** |
| Human | chronic HCV infection | CD11b+ HLA-DRlo CD33+ CD14+ | Inhibition of T cell proliferation and IFN production | Arginase1 | [6] |
| Human | HCV-infected hepatocytes | CD11b+/lo HLA-DRlo/- CD33+ CD14+ | Inhibition of T cell cytokine production | ROS  Cell-cell-contact | [7] |
| Human | HCC | CD11b+ HLA-DR- CD33+ CD14- | Long-lasting inhibition of effector T cells |  | [22-30] |
| Human | HCC | HLA-DRlo/- CD14+ | Inhibition of natural killer cells | Cell-cell-contact  NKp30 | [33] |
| Human | HCC | HLA-DRlo/- CD14+ | Induction of Treg and inhibition of effector T cells | arginase | [29] |
| Mouse | CCl4-mediated fibrosis | CD11b+Ly6G-Ly6ChiF4/80+  CD11b+Ly6G+Ly6CloF4/80- | Amelioration of fibrosis through inhibition of HSC | IL-10 production | [13] |
| Mouse | Th1-mediated inflammation | CD11b+Ly6G-Ly6Chi  CD11b+Ly6G+Ly6Clo | Inhibition of T cell proliferation (CD4+ and CD8+) | iNOS  cell-cell-contact | [48] |
| Mouse | Sepsis | CD11b+Gr1+ | Inhibition of IL-12 and induction of IL-10 release by macrophages | Cell-cell-contact | [2] |
| Mouse | Immune-mediated hepatitis | CD11b+Ly6GloLy6Chi  CD11b+Ly6G+Ly6Clo | Suppression of CD4+ T cell proliferation | iNOS | [46,47] |
| Mouse | ConA-mediated hepatitis | CD11b+Ly6G-Ly6C+  CD11b+Ly6G+Ly6C+(int) | Protection against liver injury through inhibition of T cells | arginase | [4] |
| Mouse | ConA/LPS-mediated hepatitis | CD11b+Ly6GloLy6Chi  CD11b+Ly6GhiLy6Cint | Suppression of CD4+ T cell proliferation and cytokine production | iNOS  cell-cell-contact | [3,45] |
| Mouse | CTL-mediated liver injury | CD11b+Gr1+ | Suppression of CTL proliferation and IFN production |  | [21] |
| Mouse | HBV (transgenics) | CD11b+Gr1+ | Suppression of HBV-specific CTL | Arginase  iNOS | [5] |
| Mouse | HCC/primary liver tumors | CD11b+Gr1+ | Suppression of anti-tumor CTL |  | [35,36,38] |
| Mouse | Gastrointestinal cancer with liver metastasis | CD11b+Gr1+/int | Inhibition of T cell proliferation and tumor cell lysis |  | [40] |

ConA: Concanavalin A; CTL: Cytotoxic T lymphocyte; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; IFN: Interferon; IL: Interleukin; iNOS: Inducible nitric oxide synthase; ROS: Reactive oxygen species; Treg: Regulatory T cell; MDSC: Myeloid derived suppressor cells.



**Figure 1 Myeloid derived suppressor cells in liver disease.** Left: Myeloid derived suppressor cells (MDSC) accumulate during infectious, inflammatory or malignant diseases in several compartments of the body, including the liver. MDSC potently suppress immunogenic T cell responses, which is also relevant for liver diseases such as hepatic inflammation, fibrosis or hepatocellular carcinoma (HCC); Right: The induction of monocytic (mMDSC) or granulocytic (gMDSC) MDSC in the liver is promoted by different cell types in the liver *via* cell-cell-contact dependent mechanisms (*e.g*., CD44) as well as *via* various soluble mediators. Details are provided in the main text. GM-CSF: Granulocyte-macrophage colony-stimulating factor; HCC: Hepatocellular carcinoma; hepa: Hepatocyte; HGF: Hepatocyte growth factor; HSC: Hepatic stellate cell; IL: Interleukin; SAA: Serum amyloid A; TC: T cell.