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

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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, including 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; Liver cirrhosis; Macrophage; Hepatitis C virus

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and accumulation, and recent studies linked these cells to the pathogenesis of hepatic inflammation, fibrosis and hepatoacellular 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 antitumoral immunity, but their involvement in hepatic fibrosis is less clear. Thus, modulating MDSC functionality might represent a promising novel therapeutic target for liver diseases.

Hammerich L, Tacke F. Emerging roles of myeloid derived suppressor cells in hepatic inflammation and fibrosis. World J Gastroenterol 2015; 6(3): 43-50 Available from: URL: http://www.wjgnet.com/2150-5330/full/v6/i3/43.htm DOI: http://dx.doi.org/10.4292/wjgp.v6.i3.43

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 appear 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 such as 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 Ly6Ghi Ly6Chi, gMDSC are Ly6Glo Ly6C+ 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 include L-arginine depletion by the enzymes arginase 1 (Arg1) or inducible nitric oxide synthase (iNOS) and generation of reactive oxygen species (ROS)[6,10,12]. 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[16] 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[17], 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[18]. 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-DR+ 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[19,20]. However, this induction seems to be mediated by soluble factors rather than cell-cell contact. Chou et al[20] 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\(^\text{[20]}\). 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\(^\text{[20]}\).

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\(^\text{[2]}\). 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\(^\text{[2]}\). Consistently, the ectopic expression of IL-6 in the liver induced accumulation of MDSC in liver and spleen, which protected mice from CD8\(^+\) T cell-mediated liver injury\(^\text{[21]}\).

Another factor that may contribute to 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-1\(\beta\) 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\(^\text{[22,23]}\). This may also apply to liver diseases as inflammasome activation is important in a wide range of conditions\(^\text{[24,25]}\). 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\(^\text{[26,27]}\). 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\(^\text{[28]}\), 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\(^\text{[6,7,29-32]}\). Human MDSC in HCC patients are mainly CD14\(^+\) HLA-DR\(^+\) and able to inhibit T cell proliferation in an arginase dependent manner\(^\text{[29]}\). Furthermore, these cells induce a regulatory phenotype in CD4\(^+\) T cells and inhibit natural killer (NK) cell function \textit{in vitro}\(^\text{[29,33]}\). Likewise, MDSC in the blood of patients...
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-DR40 CD33+ CD14+ | Inhibition of T cell proliferation and IFNγ production | Arginase1  <br> ROS  <br> Cell-cell-contact | [6]  
| Human            | HCV-infected hepatocytes | CD11b+ HLA-DR40, CD33+, CD14+ | Inhibition of T cell cytokine production | Arginase1  <br> ROS  <br> Cell-cell-contact | [7]  
| Human            | HCC                      | CD11b+ HLA-DR CD33+ CD14+ | Long-lasting inhibition of effector T cells <br> Inhibition of natural killer cells | Cell-cell-contact  <br> Arginase  <br> IL-10  production | [22-30]  
| Human            | HCC                      | CD11b+ HLA-DR CD33+ CD14+ | Inhibition of T cell proliferation (CD4+ and CD8+) | Cell-cell-contact  <br> Arginase  <br> IL-10  production | [33]  
| Mouse            | CCl-induced fibrosis     | HLA-DR40 CD11b+ | Induction of Treg and inhibition of effector T cells  <br> Amelioration of fibrosis through inhibition of HSC | Arginase  <br> IL-10  production | [29]  
| Mouse            | Immune-mediated hepatitis | CD11b+Ly6G/Ly6C F4/80 | Suppression of CD4+ T cell proliferation | Arginase  <br> IL-10  production | [46,47]  
| Mouse            | ConA-mediated hepatitis  | CD11b+Ly6G/Ly6C F4/80 | Protection against liver injury through inhibition of T cells | Arginase  <br> IL-10  production | [4]  
| Mouse            | ConA/LPS-mediated hepatitis | CD11b+Ly6G/Ly6C F4/80 | Suppression of CD4+ T cell proliferation and cytokine production | Arginase  <br> IL-10  production | [3,45]  
| Mouse            | CTL-mediated liver injury | CD11b+Ly6G/Ly6C F4/80 | Suppression of CTL proliferation and IFNγ production | Arginase  <br> IL-10  production | [21]  
| Mouse            | HCC/primary liver tumors | CD11b+Ly6G/Ly6C F4/80 | Suppression of anti-tumor CTL | Arginase  <br> IL-10  production | [5]  
| Mouse            | Gastrointestinal cancer  | CD11b+Ly6G/Ly6C F4/80 | Inhibition of T cell proliferation and tumor cell lysis | Arginase  <br> IL-10  production | [35,36,38]  

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.

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

with chronic HCV were shown to be CD11b+ HLA-DR40 CD14+ CD33+ and suppress T cells using arginase[6]. In addition, ROS production may 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[38]. 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 et al[48] 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. 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[49] demonstrated recently that TLR2-deficient mice develop more aggressive HCC than wildtype (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 may 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 monocytic-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 cannabinoids[48] or IL-25[49] increases the number of hepatic CD11b+ Gr1- cells that ameliorate 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[40]. 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, the 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 et al[45] 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. 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 micro-environment, 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 profibrotic 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[49].

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 adaptively 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.

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