Review Article

The Dual Role of Myeloid-Derived Suppressor Cells in Liver Pathologies

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Abstract

Myeloid-derived Suppressor Cells (MDSCs) are a heterogeneous population of cells that expands during infection, inflammation and cancer and has the ability to suppress T-cell responses. Therefore these cells constitute a unique component of the immune system that regulates immune responses not only in healthy individuals but also in the context of various diseases, including acute and chronic liver pathologies as well as hepatocellular carcinoma. In this article, we review the available data on the distribution and function of MDSCs in liver diseases and discuss whether and how the properties of these cells could be manipulated for therapeutic purposes.

ABBREVIATIONS

MDSCs: Myeloid-Derived Suppressor Cells; HSC: Hepatic Stellate Cells; IL-10: Interleukin-10; TGF-β1: Transforming Growth Factor-β1; Tregs: Regulatory T Cells; ROS: Reactive Oxygen Species; CH: Chronic Hepatitis; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; RVR: Rapid Virologic Response; EVR: Early Virologic Response; HBV: Hepatitis B Virus; FH: Fulminant Hepatitis; D-Gal: D-Galactosamine; ConA: Concanavalin A; CBD: Cannabidiol; FXR: Farnisoid X Receptor.

INTRODUCTION

The liver has unique immune regulatory functions that promote the induction of tolerance rather than responses to antigens encountered locally [1]. The liver tolerogenic property was initially demonstrated by spontaneous acceptance of liver transplants in mice without requirements of immunosuppression, and in human beings, weaning off immunosuppression can be obtained for at least one year in nearly one fifth of liver transplant recipients [2]. In contrast, hepatocyte transplants are rapidly destroyed through a process that is immunologically-mediated, while hepatocytes survive indefinitely in syngeneic recipients and allogeneic SCID recipients, thus suggesting that local immune-suppressive mechanisms help prevent hepatocyte damage [3]. Indeed, liver contains enzymes that influence negatively the function of lymphocytes, such as tryptophan-2,3-deoxygenase, which converts tryptophan into immune regulatory molecules (i.e. N-formyl-kynurenine), and arginase, which metabolizes arginine [1]. Moreover, Kupffer cells and Hepatic Stellate Cells (HSC) produce interleukin (IL)-10 or Transforming Growth Factor (TGF)-β1 respectively thus contributing to inhibit local T cell responses [4,5]. Consistently, co-transplantation of hepatocytes with HSC in mice results in long-term survival of allografts without requirement of immunosuppression [3]. The HSC-mediated inhibition of the tissue-damaging immune responses relies also on the ability of these cells to promote CD8+ T cell apoptosis [6], increase the fraction of Foxp3+ regulatory T cells (Tregs) [7,8] and induce the differentiation of Myeloid-Derived Suppressor Cells (MDSCs) [3,9], a class of cells with regulatory properties initially identified in cancer patients and supposed to contribute to cancer evasion from immune surveillance [3]. MDSCs are a heterogeneous population of myeloid cells consisting of progenitor and immature myeloid cells [10,11]. In mice, MDSCs co-express the myeloid-cell lineage differentiation antigens CD11b and Gr1, with the later having two different epitopes, Ly6G and Ly6C that help identify two MDSCs subsets: granulocytic MDSCs with a CD11b+ Ly6G+Ly6C-low phenotype and monocytic MDSCs with a CD11b+Ly6G-Ly6C-high phenotype [12,13]. Functionally, MDSCs suppress T-cell responses via numerous mechanisms, including cysteine deprivation [14], up-regulation of Reactive Oxygen Species (ROS) [15,16], production of nitric oxide [11] and increased metabolism of the amino acid L-arginine through the expression of arginase-1 [17,18]; this latter pathway down-regulates CD3+ T cell receptor ζ expression and inhibits T cell proliferation [19]. Moreover, MDSCs promote Treg cell induction and expansion [20,21]. MDSCs accumulate not only within the tumor but also in lymphoid organs (e.g. spleen and bone marrow) and peripheral blood circulation [22]. The liver has recently been shown to be a preferred site for homing and expansion of MDSCs during infectious and neoplastic diseases [23].

In this article we review the data available on the dual role of MDSCs in liver pathologies and discuss whether and how the properties of these cells could be manipulated for therapeutic purposes.

Myeloid-derived suppressor cells in chronic hepatitis

Chronic hepatitis (CH) is one of the main causes of liver cirrhosis and Hepatocellular Carcinoma (HCC) worldwide [24]. Hepatitis C Virus (HCV) infection is the main cause of CH, as approximately 130-200 milions of individuals are chronically infected with HCV [25]. In HCV-infected patients, the viral RNA load remains high during the first weeks of infection and declines after 6-8 weeks, in parallel to the appearance of virus-specific CD8+ T cells in the peripheral blood [26-28]. In contrast, in patients with CH, HCV-specific CD8+ T cell responses are typically weak and can often be lost due to viral escape mutations or suppression by regulatory mechanisms [27,29,30]. Emerging evidence indicates that MDSCs can drive the liver disease progression in CH given their ability to down-regulate T cell function [29]. Zeng and colleagues determined the frequency of CD33+CD11b+Lin1−HLA-DR- MDSCs in the peripheral blood of 61 treatment-naive patients with HCV-related CH, 14 patients undergoing pegylated-interferon-α/ribavirin therapy who developed a Rapid Virologic Response (RVR) and 22 patients who developed an Early Virologic Response (EVR) [31]. A significantly higher frequency of MDSCs was seen in treatment-naïve patients compared to healthy controls, patients with RVR or patients with EVR, and there was a significant positive correlation between the frequency of MDSCs and HCV RNA load. Immunohistochemical analysis revealed that arginase-1-positive cells accumulated in the livers of CH patients, and the number of such cells was strictly associated with the extent of inflammatory injury [31]. Consistent with the ability of MDSC-derived arginase-1 to deplete L-arginine in CD8+ T cells and, hence, to down-regulate CD3 ζ and inhibit T cell function, lymphocytes infiltrating the livers of CH patients had reduced expression of CD3 ζ, a phenomenon that was reverted by the in vitro treatment of lymphocytes with exogenous L-arginine. In patients who achieved either RVR or EVR, there was a decreased frequency of MDSCs, which correlated positively with the HCV RNA load decline and negatively with TCR ζ expression on CD8+ T cells [31]. Collectively, these findings are in line with another report showing that frequency of MDSCs was increased in the peripheral blood of treatment-naïve HCV-related CH patients and correlated with plasma HCV-RNA, blood aminotransferase, and activated T cells, and was decreased by successful therapy [32]. In contrast, a recent paper documented no difference in terms of MDSC frequency between HCC patients and healthy controls [33].

Studies by Tacke and colleagues suggest that HCV by itself could favor development of MDSCs, as hepatocytes infected with HCV clone, JFH-1, induce human CD33+ monocytes to differentiate in MDSCs, which exhibit up-regulation of p47phox, a component of the nitrogen oxide 2 complex involved in ROS production [16]. ROS-producing MDSCs, which express high levels of p47phox, accumulate in the peripheral blood of chronically HCV-infected individuals and extracellular HCV core-induced MDSCs suppress autologous T-cell proliferation and IFN-γ production following TCR stimulation [16]. Taken together these findings raise the intriguing possibility that differentiation of MDSCs is one of the mechanisms by which HCV evades the host's immune response.

Little is known about the frequency and function of MDSCs in Hepatitis B Virus (HBV) infection. Studies in HBV transgenic mice, a murine model of chronic HBV carrier state, documented increased frequency of MDSCs in the livers of infected animals as compared to normal mice, and MDSCs suppressed the proliferative capacities of allogeneic T cells and HBV surface antigen-specific lymphocytes through alteration of T cell antigens and impairment of interferon-γ production [34].

MDSCs in liver cancer

MDSCs represent nearly one third of the normal bone marrow cells and less than 3% of all nucleated splenocytes in tumor-free mice but expand in cancer-bearing mice and accumulate markedly in the livers of tumor-bearers [23,35]. Such an accumulation is seen in mice with both primary and secondary liver tumors and their appearance in the liver accelerates the formation of liver metastasis [23,36]. MDSCs expressing CD14 but little or no HLA-DR and having high arginase activity are significantly increased in peripheral blood and tumoral areas of patients with HCC [37]. The frequency of MDSCs has also been correlated with tumor progression and clinical staging in HCC patients, as indicated by a significant decrease in the number of circulating MDSCs in most patients with curative treatment [37,38].

The exact mechanism underlying the recruitment of MDSCs to the liver is not fully understood but chemokines produced within the tumor microenvironment can stimulate homing of MDSCs to this organ. This does not however exclude the possibility that MDSCs could also be arising from the liver. In this context it is noteworthy, for example, that GM-CSF, which is secreted by various human and mouse cancers, expands MDSCs in the livers in the absence of a growing tumor [23].

Besides suppressing effector T cells, MDSCs have further immunological properties, which might allow liver tumors to evade immune system. These include differentiation of cells with immunoregulatory properties (i.e. type 2 macrophages, Tregs, and IL-10-secreting T cells) [37,39], inhibition of NK cell cytotoxicity and cytokine production through cell-cell dependent contact mechanisms with the NK receptor, NKp30 [40]. Moreover, expression of membrane bound-TGF-β on MDSCs, and not Tregs, contributes to reduce IFN-γ expression, NKG2D and cytotoxicity by NK cells [35]. Consistently, the impaired function of hepatic NK cells in orthotopic liver cancer-bearing mice can be restored by depletion of MDSCs, but not Tregs [35].

The protective role of MDSCs in immune-mediated liver diseases

Studies in experimental models of immune-mediated liver pathologies indicate that MDSCs may play a protective role in Fulminant Hepatitis (FH) (also termed fulminant liver failure or acute liver failure). FH is the clinical manifestation of sudden and severe hepatic injury, which arises from many causes, including viruses, drugs and toxins, and may result in severe impairment of liver function, followed by hepatic encephalopathy, and progressive multiorgan failure [41]. Histopathologically, FH is characterized by diffuse intrahepatic infiltration by T cells with massive multilobular necrosis. Although mouse models of acute liver injury, such as those induced by administration of hepatotoxins [e.g. D-Galactosamine (D-Gal)] [42] or injection of

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T cell-activating substances [e.g. concanavalin A (ConA)] [43], do not exactly recapitulate the pathogenic alterations of FH, they have contributed to show that macrophages, NK cells, NKT cells and T cells all play a crucial role in experimental liver injury, and attenuation of experimental FH can be accomplished by targeting such cells [44]. In this context, we have recently shown that human FH associates with a reduced synthesis of IL-25 [45], a member of the IL-17 cytokine gene family that delivers negative signals to macrophages/dendritic cells with the downstream effect of suppressing Th1- [46] and Th17-mediated [47] inflammatory responses in various organs. Similarly, liver production of IL-25 was reduced in mice with acute liver injury induced by activation of liver macrophages and T cells via the systemic administration of D-Gal+LPS or ConA respectively, and such a reduction was paralleled by enhanced synthesis of inflammatory cytokines, such as IL-6 and TNF [45]. Treatment of mice with recombinant IL-25 prevented liver damage in both models, and this counter-regulatory effect was associated with a significant increase in the number of Gr1/CD11b-expressing MDSCs [45]. MDSCs isolated from IL-25-treated mice given D-Gal/LPS restrained T cell activation in vitro thus confirming their suppressive nature. Consistently, depletion of such cells from mice abolished the IL-25-mediated protection against D-Gal/LPS-induced liver damage [45].

The molecular mechanism by which IL-25 promotes accumulation of MDSC in the livers of mice with FH remains to be ascertained, even though it is conceivable that IL-25 induces the synthesis of chemokines (i.e. CCL17), which could promote the recruitment of MDSCs from the periphery during FH [45].

Hegde and colleagues demonstrated that cannabidiol (CBD), a natural non-psychoactive cannabinoid, inhibited ConA-induced hepatitis and increased the number of arginase-expressing CD11b/Gr-1-positive MDSCs in the liver [48]. Purified CBD-induced MDSCs were able to suppress T cell proliferation in vitro in an arginase-dependent manner and protected mice from ConA-induced liver injury following adoptive transfer into naïve mice [48]. CBD failed to induce MDSCs and suppressed ConA-induced hepatitis in the livers of vanilloid receptor-deficient mice, thus suggesting that CBD primarily acted via this receptor to induce MDSCs [48]. The ability of CBD to induce MDSCs and suppress hepatitis was also demonstrated in Staphylococcal enterotoxin B-induced liver injury [48]. Along the same line was the demonstration that activation of farnesoid X receptor (FXR), a highly expressed hepatic nuclear bile acid receptor that regulates expression of genes involved in liver homeostasis and immune regulation, reduced acute liver injury induced by ConA and D-Gal/Cer and such a treatment produced a robust expansion of MDSCs in the liver [49]. A protective role of MDSCs in the liver has been documented in further models of acute liver injury, such as that seen in mice deficient in the gene encoding TGF-β1 [50].

CONCLUDING REMARKS

The data discussed in this article highlight the critical role of MDSCs in the control of immune responses in the liver in both healthy and pathological conditions and suggest that manipulation of MDSCs may have therapeutic implications. Since MDSCs suppress immunity against tumors and their accumulation in the liver negatively affects the course of HCC,

treatments eliminating MDSCs themselves or targeting MDSC-derived suppressive factors, such as antibody depletion of Gr1 cells, chemotherapeutic drugs or retinoic agents, could improve the efficacy of anti-cancer compounds [34,37,40]. In this context, for example, it has been demonstrated that the administration of anti-c-Kit antibody to mice bearing MCA26 colon carcinoma cells in the liver resulted in a dramatic enhancement in T cell proliferation, which was associated with reduced numbers of MDSCs and Tregs in the bone marrow and spleen and reduced angiogenesis [51]. The modulation of MDSCs for the reversal of tolerogenic responses could be beneficial not only in a malignancy setting but can be exploited to boost T cell responses against HVC-related CH and facilitate virus clearance [28]. In designing therapeutic interventions around MDSCs, some relevant issues need however to be taken into consideration. Approaches that directly target MDSC within the liver microenvironment could amplify T cell-dependent immune signals that eventually cause liver damage (e.g. FH, autoimmune hepatitis). Moreover, a more detailed analysis of mediators of immune-suppression in HCC showed that the increased frequency of MDSCs was associated with increased numbers of Tregs and enhanced production of immunosuppressive cytokines [52]. This suggests that multiple, and not single, immune-regulatory defects contribute to dampen the host immune response against HCC. Indeed, in vitro studies showed that activation of effector T cells of HCC patients was improved only whether both MDSCs and Tregs were depleted [52]. We also feel that further experimentation will be needed to better determine at which stage of either CH or HCC these immune-regulatory cells act and which factors/mechanisms promote their accumulation in the liver. Similarly, more work will be necessary to ascertain whether MDSC frequency in the blood is an useful tool for predicting the responsiveness to therapy and prognosis of the patients. Finally, the recent demonstration that MDSCs are induced in mice with carbon tetrachloride-induced liver fibrosis [53] suggests the necessity of further studies to evaluate whether these cells may be beneficial in the prevention of cirrhosis.

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