Published in final edited form as:
Int Immunopharmacol. 2011 July ; 11(7): 789–793. doi:10.1016/j.intimp.2011.01.026.

MDSC in Autoimmunity

James G. Cripps[1] and **James D. Gorham**[1,2]

[1]Department of Microbiology & Immunology, Dartmouth Medical School, Lebanon, NH 03756

[2]Department of Pathology, Dartmouth Medical School, Lebanon, NH 03756

Abstract

Myeloid derived suppressor cells (MDSC) were first described nearly two decades ago. Until recently, however, descriptions of MDSC populations were found almost exclusively in animal models of cancer or in cancer patients. Over the last few years, an increasing number of reports have been published describing populations of myeloid cells with MDSC-like properties in murine models of autoimmune disease. In contrast to the proposed deleterious role of MDSC in cancer - where these cells likely inhibit tumor immunity - in the context of autoimmunity, MDSC have the potential to suppress the autoimmune response, thereby limiting tissue injury. A logical corollary of this hypothesis is that a failure of endogenous MDSC to appropriately control autoimmune T cell responses *in vivo* may actually contribute to the pathogenesis of autoimmune disease.

Introduction

Although MDSC were originally described in the contexts of murine tumor models and cancer patients, it has become appreciated over the last few years that MDSC participate in a variety of inflammatory immune responses, such as parasitic infections (1) and, more recently, autoimmunity (2). While MDSC are posited to play deleterious roles in cancer and infection, functional MDSC may, in theory at least, serve a beneficial role in organ-specific autoimmunity, by limiting T cell mediated inflammation and harmful pathology. MDSC in autoimmunity have been studied almost exclusively in the context of the laboratory mouse. There are few studies in patients with autoimmunity, and additional research is needed to determine the role, if any, of MDSC immune responses in human autoimmune disease. We will thoroughly review available studies from mouse models, focusing on three organ systems (brain, gut, and liver) and briefly describe findings from additional model systems of autoimmunity in other organs, then discuss possibilities for utilizing MDSC as a therapeutic modality in autoimmunity. For thorough reviews of MDSC biology, readers are referred to other articles appearing in this issue of *International Immunopharmacology*.

MDSC and autoimmunity in the central nervous system (CNS)

While research into the role of MDSC in autoimmunity is in its relative infancy, several studies of MDSC in CNS autoimmunity have been published in the last few years. Experimental autoimmune encephalomyelitis (EAE) is a commonly used mouse model of multiple sclerosis (MS), an autoimmune inflammatory disease of the CNS characterized by recurrent bouts of T cell mediated attack upon antigens in neuronal myelin sheaths. EAE can be induced by immunization of susceptible mice with myelin proteins (or peptides) along

with adjuvant. Myelin-specific T cells are activated in the periphery and migrate into the CNS, where, through elaboration of inflammatory cytokines and chemokines, they cause demyelination and CNS damage, resulting in progressive neurologic pathology culminating in paralysis. It has been recognized since at least 1997 that T cell inflammation in the CNS is accompanied by the recruitment from the periphery of myeloid cells (3-5) and recent papers have examined the possible role of $CD11b^{+}Ly\text{-}6C^{hi}$ cells in disease. Zhu et al. showed that $CD11b^{+}$ cells accumulate in blood, spleen, and CNS in mice following induction of EAE. A sub-population of myeloid cells isolated from spleen bearing a "monocytic" cell surface phenotype ($CD11b^{+}Ly\text{-}6C^{high}Ly\text{-}6G^{-}$) potently suppressed the proliferation of both $CD4^{+}$ T cells and $CD8^{+}$ T cells *ex vivo*, via induction of T cell apoptosis that was mediated by nitric oxide (6). While the kinetics of $CD11b^{+}Ly\text{-}6C^{high}Ly\text{-}6G^{-}$ cell accumulation positively correlated with the mouse EAE clinical score/disease severity, this study did not directly address the specific role of $CD11b^{+}Ly\text{-}6C^{high}Ly\text{-}6G^{-}$ cells *in vivo*, rendering the significance of the *ex vivo* observations uncertain. Indeed, other studies suggest that $CD11b^{+}Ly6C^{+}$ cells may actually contribute to CNS damage. Mice deficient in CCR2 exhibit reduced accumulation of myeloid cells in inflamed tissue, and develop milder EAE disease (4,7). Complicating the interpretation of this finding is the fact that CCR2 is expressed on multiple cell types, including not only myeloid cells such as monocytes and DC, but also basophils, some T cells, as well as brain parenchymal cells such as neurons, astrocytes, and endothelia (8,9). Mildner et al. used bone marrow chimera approaches to convincingly demonstrate that CCR2 expression on radio-sensitive, non-lymphoid cells (i.e. myeloid cells) was particularly important for maximum EAE pathology. Decreased pathology was associated with a reduction in the accumulation of $CD11b^{+}Ly\text{-}6C^{hi}$ monocytes in the CNS, suggesting that this cell population serves as pathologic effectors of disease, rather than suppressor cells (10). King et al. found in a model of remitting/relapsing EAE in SJL mice that $CD11b^{+}Ly\text{-}6C^{hi}$ cells accumulate in blood and CNS prior to and during the onset of flares of EAE in myelin-immunized SJL mice. A single application of clodronate liposomes to mice, which depletes actively phagocytic macrophages and results in enhanced recruitment of $CD11b^{+}Ly\text{-}6C^{hi}$ cells from the bone marrow (11), caused exacerbation of EAE in SJL mice that had received an adoptive transfer of encephalitogenic T cells. These blood $CD11b^{+}Ly\text{-}6C^{hi}$ cells migrated into the CNS where they matured into macrophages and DCs. The authors concluded that $CD11b^{+}Ly\text{-}6C^{hi}$ cells enhance EAE, following their maturation into functional DCs and/or inflammatory macrophages (12).

EAE can also be induced in susceptible mouse strains some three weeks following infection with Theiler's murine encephalomyelitis virus (TMEV), a natural mouse pathogen that results in demyelinating disease (13). In this model system, $CD11b^{+}Ly\text{-}6C^{+}$ cells infiltrated the CNS early in disease, concomitant with the innate immune response phase of the disease, but waned after one week. Treatment of mice to deplete the $CD11b^{+}Ly\text{-}6C^{+}$ cell population, using either anti-Gr1 mAb, or the more specific anti-Ly-6C mAb, caused a reduction in EAE pathology. While at first glance this result may indicate an immune activating role for $CD11b^{+}Ly\text{-}6C^{+}$ cells, additional experiments suggested an immune suppressive role. Specifically, depletion of $CD11b^{+}Ly\text{-}6C^{+}$ cells caused higher expression of inflammatory cytokines in CNS, as well as a significant increase in TMEV-specific T cell responses. The authors concluded that the apparent contribution of $CD11b^{+}Ly\text{-}6C^{+}$ cells to EAE was a secondary phenomenon, due to suppressive effects of $CD11b^{+}Ly\text{-}6C^{+}$ cells on virus-specific immunity (14). However, a direct suppressive effect of $CD11b^{+}Ly\text{-}6C^{+}$ cells on T cells was not demonstrated, and specific mechanisms explaining the suppression were not explored further.

Indeed, none of these studies appears to be definitive. The Zhu study examined *in vitro* effects of $CD11b^{+}Ly\text{-}6C^{hi}$ cells on T cells, but did not examine their possible *in vivo*

participation in EAE pathology. Conversely, the Mildner study and the King study drew associations *in vivo* between $CD11b^{+}Ly\text{-}6C^{hi}$ cell accumulation and disease, but did not test the ability of these cells to serve as MDSC either *in vitro* or *in vivo*. Interestingly, in the King study, the transit of $CD11b^{+}Ly\text{-}6C^{hi}$ cells from blood into CNS was associated with a 1000-fold increase in the expression of iNOS mRNA (12), an intriguing observation with respect to possible MDSC function. It seems likely that $CD11b^{+}Ly\text{-}6C^{hi}$ cells have multiple roles in EAE, serving both pro-inflammatory functions and anti-inflammatory functions. This population of cells is both heterogenous and plastic (15,16), so that specific cues in the microenvironment will preferentially activate specific subsets, functions, and pathways of differentiation. In this regard, it is interesting that blood $CD11b^{+}Ly6G^{-}Ly6C^{+}$ monocytes from naïve mice were observed in a recent study to exhibit T cell suppressor activity *in vitro*, mediated in part by NO (17). After induction of EAE, however, blood $CD11b^{+}Ly6G^{-}Ly6C^{+}$ cells exhibited partially reduced suppressive activity. This study did not examine the function of $CD11b^{+}Ly6C^{+}$ cells in the CNS, however, and loss of suppressor function may simply be due to the migration of a more suppressive subset of $CD11b^{+}Ly6C^{+}$ cells from blood into the CNS. Nevertheless, this observation supports a role for the microenvironment (i.e. inflammatory state) in determining the specific functionality of $CD11b^{+}Ly6C^{+}$ cells in the context of autoimmune CNS disease.

MDSC and autoimmunity in the gut

Inflammatory Bowel Disease (IBD) encompasses several diseases, including Crohn's disease and ulcerative colitis. Haile et al. have recently convincingly described the development of a MDSC population in a mouse model of IBD. In this particular model IBD is induced in transgenic mice harboring enterocyte-specific expression of hemagglutinin (HA) after a single adoptive transfer of HA-specific $CD8^{+}$ T cells (CL4-TCR) (18). Interestingly, two transfers of CL4-TCR cells, separated by an interval of 12 days, renders mice tolerant to enterocolitis at a third CL4-TCR cell adoptive transfer. Three CL4-TCR transfers caused a substantial induction of a population of $CD31^{+}CD11b^{+}Gr1^{+}Ly\text{-}6C^{+}$ cells in both spleen and intestine. This cell population suppressed $CD8^{+}$ T cell proliferation *ex vivo* by induction of T cell apoptosis through a mechanism that required NO (19). Unfortunately, whether $CD11b^{+}Gr1^{+}$ cells were required *in vivo* for the development of the tolerant state after two CL4-TCR transfers was not tested in this study. However, isolated $CD11b^{+}Gr1^{+}$ cells did effectively prevent colitis when administered to HA-transgenic mice receiving the first transfer of CL4-TCR cells (19), thus showing that $CD11b^{+}Gr1^{+}$ are sufficient for protection; whether they are necessary remains to be determined. Interestingly, peripheral blood from IBD patients exhibited increased an increased frequency of cell populations with a surface phenotype ($CD14^{+}HLA\text{-}DR^{-/low}$) suggestive of an MDSC population (19). It is worth mentioning here that this same group of investigators has recently showed that the adhesion protein CD49d is expressed specifically on “monocytic” MDSC populations in the mouse enterocyte-HA model system, as well as in murine cancer models (20). It remains to be determined whether CD49d also marks monocytic MDSC in humans, which, if demonstrated, would be a technical advance, as human cells do not express Gr1, Ly6G, or Ly6C.

MDSC and autoimmunity in the liver

The liver appears to have an important, albeit incompletely defined, role in MDSC biology. The liver is the major source of acute-phase proteins (APP), an evolutionarily conserved family of proteins produced principally in liver in response to inflammation. A recent study demonstrates that hepatocyte-specific gp130-STAT3 signaling in mice protects against excessive inflammation during sepsis. Protection is mediated by gp130-mediated APP production (specifically, serum amyloid A (SAA) and the CXCL chemokine KC), and subsequent mobilization and accumulation of MDSC, that in turn function to inhibit

pathologic inflammation (21). MDSC preferentially accumulate in liver in tumor-bearing mice (22), indicating the existence of specific (as yet uncharacterized) biological mechanisms driving this process. Furthermore, as observed with other solid tumors, hepatocellular carcinoma in patients is associated with an elevated frequency of circulating $CD14^{+}HLA\text{-}DR^{-/low}$ myeloid cells with suppressor properties (23,24).

Autoimmune hepatitis (AIH) is a liver-specific autoimmune disease in which T cells expressing IFN-γ accumulate in liver portal tracts and in liver parenchyma (25,26), and cause hepatocellular damage and liver necrosis (27). Over the last decade we have developed and extensively characterized a relevant mouse model of AIH: mice with a targeted deficiency in the gene encoding the immunoregulatory protein TGF-β1 and bred onto a BALB/c background spontaneously develop an acute $CD4^{+}$ T cell mediated autoimmune liver disease (28,29) that depends on IFN-γ (30). Recently, we demonstrated that $CD4^{+}$ T cell accumulation in the BALB/c *Tgfb1*$^{-/-}$ liver is accompanied by an accumulation of $CD11b^{+}Gr1^{+}$ myeloid cells (31). Isolated $CD11b^{+}Gr1^{+}$ myeloid cells from BALB/c *Tgfb1*$^{-/-}$ livers readily suppressed $CD4^{+}$ T cell proliferation *ex vivo*, via a mechanism that depended on nitric oxide, IFN-γ, and cell-cell contact. Inhibition was specifically associated with the monocytic ($Ly\text{-}6C^{+}$) subset of myeloid cells. We demonstrated a particularly important role for IFN-γ in the development of this MDSC population, as mice doubly deficient in the *Tgfb1* gene as well as the *Ifng* gene did not accumulate an excess of $CD11b^{+}Gr1^{+}$ cells in the liver. Moreover, resident liver $CD11b^{+}Gr1^{+}$ cells isolated from *Ifng*$^{-/-}$*Tgfb1*$^{-/-}$ mice completely lacked suppressor activity (31). These findings demonstrate that Th1 cells, through the release of IFN-γ, drive the accumulation of a regulatory myeloid cell population to a site of inflammation pathology.

The existence of MDSC in AIH patients has yet to be demonstrated. Interestingly, it has been long recognized from liver biopsies that $CD11b^{+}$ cells accumulate in liver during AIH flares (32). Moreover, recent work has identified an increased population of “highly activated” monocytes in the circulation of AIH patients (33), and their presence accompanies that of liver-antigen-specific T cells producing high levels of IFN-γ (34). We have previously suggested that this monocytic population may in fact represent circulating MDSC (31).

Taken together, the data available from mouse models and human AIH suggest that IFN-γ has a multifunctional role in inflammatory liver disease. On the one hand, IFN-γ mediates liver injury, as *Tgfb1*$^{-/-}$ mice lacking IFN-γ are resistant to T cell mediated attack. On the other hand, IFN-γ is essential for initiating a negative feedback pathway, through the activation and recruitment of MDSC that can potently restrain T cell proliferation. It may be predicted that, *in vivo*, MDSC play a role in mitigating liver disease in the *Tgfb1*$^{-/-}$ model system. We have directly tested this prediction. Contrary to expectations, depletion of MDSC using anti-Gr1 mAb did not exacerbate liver damage (unpublished data), consistent with the additional observations (unpublished) that freshly isolated *Tgfb1*$^{-/-}$ $CD11b^{+}Gr1^{+}$ cells do not express iNOS, and only begin to express this enzyme after co-culture *in vitro* with T cells. We discuss implications arising from this observation below in the section entitled “Do MDSC help or hurt in autoimmunity?”.

MDSC and autoimmunity in other organs

We briefly review additional reports of MDSC in other models of organ- or system-specific autoimmunity. Over ten years ago, McIntosh and Drachman described a population of “large suppressive macrophages” (LSM) in a mouse model of myasthenia gravis, a neuromuscular disorder in which antibodies specific for the acetylcholine receptor at neuromuscular junctions leads to weakness, and fatigability of skeletal muscle. *Ex vivo*, LSM induced apoptosis in activated T cells (35). MDSC have also been described in a mouse model of

experimental autoimmune uveoretinitis (EAU), an autoimmune inflammatory disease of the eye induced in mice by injection of eye-specific proteins along with adjuvant. These myeloid cells were found to resemble monocytes, expressed CD11b, and accumulated in conjunction with the progression of inflammation in the eye. *Ex vivo*, cells derived from digests of the inflamed eye inhibited the proliferation of activated T cells (36), although the mechanism of suppression was not specifically examined. Subsequent studies from this group showed that the suppressor function of MDSC in EAU requires an intact TNF response axis (37). MRL-*Fas*^{lpr} mice develop a multi-organ inflammatory disorder that resembles human systemic lupus erythematosus (SLE). A recent study identified CD11b^{+}Gr1^{low} cells in MRL-*Fas*^{lpr} mice. These cells increased in kidney and blood during disease progression and suppressed CD4^{+} T cell proliferation *ex vivo*. Interestingly, suppression was blocked by inclusion of the Arginase-specific inhibitor Nor-NOHA, indicating that Arginase, rather than iNOS, may be the principal enzyme mediating suppression by MDSC in this mouse model (38). Marhaba et al. have shown that Gr1^{+}CD11b^{+} cells can be experimentally elicited in the context of a mouse model of the autoimmune disease alopecia areata, in which inflammatory immune pathology lead to hair loss. These Gr1^{+}CD11b^{+} cells were able to inhibit T cell proliferation *in vitro* and, following *in vivo* application could cause partial restoration of hair growth (39). Finally, a recent study in a mouse model of type 1 diabetes demonstrated that MDSC isolated from tumor bearing mice were capable of abrogating CD4^{+} T cell mediated pancreatic islet damage (40). Observations from these various mouse models are summarized in Table 1.

Do MDSC help or hurt in autoimmunity?

Given the variety of activities reported for MDSC in autoimmune models (Table 1) it is a challenge to come up with a unifying hypothesis explaining their role(s) in autoimmune disease. In general, and where specifically tested, CD11b^{+}Gr1^{+} cells isolated from autoimmune inflammatory environments appear to be quite capable of inhibiting T cells in vitro, typically through the elaboration of NO and induction of T cell apoptosis, although other mechanisms have been demonstrated (e.g. arginase, CD3-zeta down-regulation). In vivo, the situation appears to be different. Where tested, endogenous MDSC appear to be rather ineffective at mitigating autoimmune disease (e.g. in the BALB-*Tgfb1*$^{-/-}$ mouse; Cripps and Gorham, unpublished), and CD11b^{+}Gr1^{+} cells (or a subset therein) may even exacerbate disease (e.g. in EAE (10-12)). By contrast, exogenously delivered MDSC can limit autoimmune pathology, as observed in mouse models of IBD (18), alopecia-areata (39), and type 1 diabetes (40) (Table 1).

To begin to reconcile these disparate findings, we speculate that there may be important differences between the activities of endogenous MDSC (those recruited to an autoimmune/inflammatory site) and those of exogenously applied MDSC (for example via adoptive transfer). By this model, endogenous MDSC are ineffective (or even disease-exacerbating), whereas exogenous MDSC are competent to inhibit disease. A mechanistic basis for this difference does not readily present itself, but may be important to understand, as it could represent the difference between help and harm. Perhaps factors within the inflammatory microenvironment “inhibit the inhibitor,” preventing pre-MDSC from realizing their suppressive potential and removal of MDSC from this “inhibitory” environment allows the suppressor phenotype to emerge, rendering them functional upon re-administration, and presumably resistant to further inhibition.

A related corollary is the hypothesis that the dysfunction of MDSC *in vivo* may be a factor driving autoimmune inflammatory pathology. MDSC accumulate in response to inflammation, but then fail to effectively down-regulate the T cell response, resulting in additional inflammation, and additional recruitment of (dysfunctional) MDSC.

Therapeutic potential of MDSC in autoimmunity

The efficacy of exogenously applied MDSC in inhibiting autoimmune disease in certain murine models suggests that they could be harnessed as a cellular therapy for autoimmune disease. We draw an analogy with regulatory T cells (T_{reg}), which suppress effector T cell responses and are being explored as a treatment modality for autoimmune disease (41). Patients with autoimmunity would donate their own cells, and MDSC would be expanded *in vitro*. There are several potential cellular sources for MDSC. In healthy subjects, approximately 5% of cells in peripheral blood have an MDSC-like phenotype (42). Recent studies have described cytokine regimens that drive *in vitro* expansion of MDSC populations isolated from peripheral blood (43). Thus, the low frequency and total numbers obtainable from peripheral blood may not be limiting in terms of potential application. *In vitro* expanded MDSC display characteristics akin to tumor isolated MDSC, including utilization of L-Arginine and contact-dependent suppression of T cells (43). Another possible source of MDSC is the bone marrow, which harbors a large reservoir of MDSC (42). Very recent studies have demonstrated efficient growth factor/cytokine-induced expansion of MDSC populations *in vitro*, utilizing bone marrow cells from either mice or human sources (44,45). In addition, recent work in mice has described MDSC populations derived from embryonic stem cells and from hematopoietic stem cells (46).

The utilization of MDSC as cellular therapy offers a new avenue of therapy for autoimmune disease. In practical application, PBMC might be isolated from the patient by leukopheresis, then MDSC expanded *in vitro* using a specific cocktail of growth factors/cytokines, and re-administered. One possibility is to “bank” MDSC for long periods of time by storage in liquid nitrogen, with the expectation that they could be re-administered during disease flares. Potential risks associated with utilizing MDSC to treat autoimmune disorders must be anticipated. First among these is that MDSC administered would not be expected to be specific for T cells recognizing autoantigens. Thus, MDSC have the potential to inhibit not only deleterious T cell responses but also protective immune responses to pathogens. Moreover, it may be difficult to direct MDSC to the organ/tissue desired. Intravenous administration of MDSC in mice results in their preferential accumulation in the liver (22). This preferential accumulation could be overcome by administration of greater numbers of MDSCs, but might result in exacerbation of “off target” T cell suppression. While liver specific accumulation could prove beneficial for treatment of autoimmune diseases of the liver, strategies for the treatment of other autoimmune diseases would need to maximize therapeutic effectiveness and limit “off-target” T cell suppression. Finally, delivery of activated myeloid cells, in spite of the expectation that they may inhibit T cells, may result in release of cytokines and other inflammatory mediators, producing flu-like symptoms, or worse yet, cytokine storm and a serum-sickness-like response. More extensive studies in animal models are needed before MDSC as cellular therapy could be entertained for a phase I trial.

Concluding remarks

MDSC participate in the immune response not only in inflammation associated with cancer, but also in other contexts, such as autoimmunity. Several mouse models of autoimmunity have described MDSC populations with the ability to suppress T cell responses. Where examined, most (but not all) of the functionally suppressive MDSC populations examined in autoimmune models can be characterized as belonging to the monocytic subset, and suppress T cell proliferation, at least *in vitro*, through iNOS and the elaboration of NO. The failure of MDSC to adequately control autoimmune T cell responses *in vivo* may contribute to the development of autoimmunity, but this hypothesis needs to be rigorously tested. The

use of *in vitro* expanded MDSC offers a promising therapeutic strategy for the treatment of human autoimmune diseases.

References

1. Van Ginderachter JA, Beschin A, De Baetselier P, Raes G. Myeloid-derived suppressor cells in parasitic infections. Eur J Immunol. 2010; 40:2976–2985. [PubMed: 21061431]
2. Nicholson LB, Raveney BJ, Munder M. Monocyte dependent regulation of autoimmune inflammation. Curr Mol Med. 2009; 9:23–29. [PubMed: 19199939]
3. Benveniste EN. Role of macrophages/microglia in multiple sclerosis and experimental allergic encephalomyelitis. J Mol Med. 1997; 75:165–173. [PubMed: 9106073]
4. Gaupp S, Pitt D, Kuziel WA, Cannella B, Raine CS. Experimental autoimmune encephalomyelitis (EAE) in CCR2(-/-) mice: susceptibility in multiple strains. Am J Pathol. 2003; 162:139–150. [PubMed: 12507897]
5. Stuve O, Youssef S, Slavin AJ, King CL, Patarroyo JC, Hirschberg DL, Brickey WJ, Soos JM, Piskurich JF, Chapman HA, Zamvil SS. The role of the MHC class II transactivator in class II expression and antigen presentation by astrocytes and in susceptibility to central nervous system autoimmune disease. J Immunol. 2002; 169:6720–6732. [PubMed: 12471103]
6. Zhu B, Bando Y, Xiao S, Yang K, Anderson AC, Kuchroo VK, Khoury SJ. CD11b+Ly-6C(hi) suppressive monocytes in experimental autoimmune encephalomyelitis. J Immunol. 2007; 179:5228–5237. [PubMed: 17911608]
7. Fife BT, Huffnagle GB, Kuziel WA, Karpus WJ. CC chemokine receptor 2 is critical for induction of experimental autoimmune encephalomyelitis. J Exp Med. 2000; 192:899–905. [PubMed: 10993920]
8. Mahad DJ, Ransohoff RM. The role of MCP-1 (CCL2) and CCR2 in multiple sclerosis and experimental autoimmune encephalomyelitis (EAE). Semin Immunol. 2003; 15:23–32. [PubMed: 12495638]
9. Banisadr G, Queraud-Lesaux F, Boutterin MC, Pelaprat D, Zalc B, Rostene W, Haour F, Parsadaniantz SM. Distribution, cellular localization and functional role of CCR2 chemokine receptors in adult rat brain. J Neurochem. 2002; 81:257–269. [PubMed: 12064472]
10. Mildner A, Mack M, Schmidt H, Bruck W, Djukic M, Zabel MD, Hille A, Priller J, Prinz M. CCR2+Ly-6Chi monocytes are crucial for the effector phase of autoimmunity in the central nervous system. Brain. 2009; 132:2487–2500. [PubMed: 19531531]
11. Tacke F, Ginhoux F, Jakubzick C, van Rooijen N, Merad M, Randolph GJ. Immature monocytes acquire antigens from other cells in the bone marrow and present them to T cells after maturing in the periphery. J Exp Med. 2006; 203:583–597. [PubMed: 16492803]
12. King IL, Dickendesher TL, Segal BM. Circulating Ly-6C+ myeloid precursors migrate to the CNS and play a pathogenic role during autoimmune demyelinating disease. Blood. 2009; 113:3190–3197. [PubMed: 19196868]
13. Olson JK, Girvin AM, Miller SD. Direct activation of innate and antigen-presenting functions of microglia following infection with Theiler's virus. J Virol. 2001; 75:9780–9789. [PubMed: 11559811]
14. Bowen JL, Olson JK. Innate immune CD11b+Gr-1+ cells, suppressor cells, affect the immune response during Theiler's virus-induced demyelinating disease. J Immunol. 2009; 183:6971–6980. [PubMed: 19890055]
15. 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. [PubMed: 21061430]
16. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009; 9:162–174. [PubMed: 19197294]
17. Slaney CY, Toker A, Flamme AL, Backstrom BT, Harper JL. Naive blood monocytes suppress T-cell function. A possible mechanism for protection from autoimmunity. Immunol Cell Biol. 2011; 89:7–13. [PubMed: 21060323]

18. Westendorf AM, Fleissner D, Deppenmeier S, Gruber AD, Bruder D, Hansen W, Liblau R, Buer J. Autoimmune-mediated intestinal inflammation-impact and regulation of antigen-specific CD8+ T cells. Gastroenterology. 2006; 131:510–524. [PubMed: 16890605]
19. Haile LA, von Wasielewski R, Gamrekelashvili J, Kruger C, Bachmann O, Westendorf AM, Buer J, Liblau R, Manns MP, Korangy F, Greten TF. Myeloid-derived suppressor cells in inflammatory bowel disease: a new immunoregulatory pathway. Gastroenterology. 2008; 135:871–881. 881 e871–875. [PubMed: 18674538]
20. Haile LA, Gamrekelashvili J, Manns MP, Korangy F, Greten TF. CD49d is a new marker for distinct myeloid-derived suppressor cell subpopulations in mice. J Immunol. 2010; 185:203–210. [PubMed: 20525890]
21. Sander LE, Sackett SD, Dierssen U, Beraza N, Linke RP, Muller 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. [PubMed: 20530204]
22. 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. [PubMed: 19549903]
23. Hoechst B, Ormandy LA, Ballmaier M, Lehner F, Kruger 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. [PubMed: 18485901]
24. 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. [PubMed: 19551844]
25. Lohr HF, Schlaak JF, Gerken G, Fleischer B, Dienes HP, Meyer zum Buschenfelde KH. Phenotypical analysis and cytokine release of liver-infiltrating and peripheral blood T lymphocytes from patients with chronic hepatitis of different etiology. Liver. 1994; 14:161–166. [PubMed: 8078396]
26. Hussain MJ, Mustafa A, Gallati H, Mowat AP, Mieli-Vergani G, Vergani D. Cellular expression of tumour necrosis factor-alpha and interferon-gamma in the liver biopsies of children with chronic liver disease. J Hepatol. 1994; 21:816–821. [PubMed: 7534321]
27. Krawitt EL. Autoimmune hepatitis. N Engl J Med. 2006; 354:54–66. [PubMed: 16394302]
28. Rudner LA, Lin JT, Park IK, Cates JM, Dyer DA, Franz DM, French MA, Duncan EM, White HD, Gorham JD. Necroinflammatory liver disease in BALB/c background, TGF-beta 1-deficient mice requires CD4+ T cells. J Immunol. 2003; 170:4785–4792. [PubMed: 12707360]
29. Robinson RT, Wang J, Cripps JG, Milks MW, English KA, Pearson TA, Gorham JD. End-organ damage in a mouse model of fulminant liver inflammation requires CD4+ T cell production of IFN-gamma but is independent of Fas. J Immunol. 2009; 182:3278–3284. [PubMed: 19234226]
30. Gorham JD, Lin JT, Sung JL, Rudner LA, French MA. Genetic regulation of autoimmune disease: BALB/c background TGF-beta 1-deficient mice develop necroinflammatory IFN-gamma-dependent hepatitis. J Immunol. 2001; 166:6413–6422. [PubMed: 11342667]
31. 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. [PubMed: 20803559]
32. Senaldi G, Portmann B, Mowat AP, Mieli-Vergani G, Vergani D. Immunohistochemical features of the portal tract mononuclear cell infiltrate in chronic aggressive hepatitis. Arch Dis Child. 1992; 67:1447–1453. [PubMed: 1489223]
33. Longhi MS, Mitry RR, Samyn M, Scalori A, Hussain MJ, Quaglia A, Mieli-Vergani G, Ma Y, Vergani D. Vigorous activation of monocytes in juvenile autoimmune liver disease escapes the control of regulatory T-cells. Hepatology. 2009; 50:130–142. [PubMed: 19437492]
34. Longhi MS, Hussain MJ, Bogdanos DP, Quaglia A, Mieli-Vergani G, Ma Y, Vergani D. Cytochrome P450IID6-specific CD8 T cell immune responses mirror disease activity in autoimmune hepatitis type 2. Hepatology. 2007; 46:472–484. [PubMed: 17559153]

35. McIntosh KR, Drachman DB. Induction of apoptosis in activated T cell blasts by suppressive macrophages: a possible immunotherapeutic approach for treatment of autoimmune disease. Cell Immunol. 1999; 193:24–35. [PubMed: 10202110]
36. Kerr EC, Raveney BJ, Copland DA, Dick AD, Nicholson LB. Analysis of retinal cellular infiltrate in experimental autoimmune uveoretinitis reveals multiple regulatory cell populations. J Autoimmun. 2008; 31:354–361. [PubMed: 18838247]
37. Raveney BJ, Copland DA, Dick AD, Nicholson LB. TNFR1-dependent regulation of myeloid cell function in experimental autoimmune uveoretinitis. J Immunol. 2009; 183:2321–2329. [PubMed: 19635911]
38. Iwata Y, Furuichi K, Kitagawa K, Hara A, Okumura T, Kokubo S, Shimizu K, Sakai N, Sagara A, Kurokawa Y, Ueha S, Matsushima K, Kaneko S, Wada T. Involvement of CD11b(+) GR-1 (low) cells in autoimmune disorder in MRL-Fas (lpr) mouse. Clin Exp Nephrol. 2010; 14:411–417. [PubMed: 20652350]
39. Marhaba R, Vitacolonna M, Hildebrand D, Baniyash M, Freyschmidt-Paul P, Zoller M. The importance of myeloid-derived suppressor cells in the regulation of autoimmune effector cells by a chronic contact eczema. J Immunol. 2007; 179:5071–5081. [PubMed: 17911592]
40. Yin B, Ma G, Yen CY, Zhou Z, Wang GX, Divino CM, Casares S, Chen SH, Yang WC, Pan PY. Myeloid-derived suppressor cells prevent type 1 diabetes in murine models. J Immunol. 2010; 185:5828–5834. [PubMed: 20956337]
41. Battaglia M, Gregori S, Bacchetta R, Roncarolo MG. Tr1 cells: from discovery to their clinical application. Semin Immunol. 2006; 18:120–127. [PubMed: 16464609]
42. Nagaraj S, Gabrilovich DI. Myeloid-derived suppressor cells. Adv Exp Med Biol. 2007; 601:213–223. [PubMed: 17713008]
43. 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. [PubMed: 20644162]
44. 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 (MDSC) inhibit graft-versus-host (GVHD) disease via an arginase-1 dependent mechanism that is upregulated by IL-13. Blood. 2010; 116:5738–5747. [PubMed: 20807889]
45. 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. [PubMed: 20605485]
46. Zhou Z, French DL, Ma G, Eisenstein S, Chen Y, Divino CM, Keller G, Chen SH, Pan PY. Development and function of myeloid-derived suppressor cells generated from mouse embryonic and hematopoietic stem cells. Stem Cells. 2010; 28:620–632. [PubMed: 20073041]

Table 1

Human Disease	Mouse model	Cell surface phenotype	Mechanism of suppression (*in vitro*)	Apparent role *in vivo*	Reference
Multiple sclerosis	EAE	$CD11b^{+}Ly\text{-}6C^{high}Ly\text{-}6G^{-}$	Nitric Oxide	Not determined	*Zhu et al*
	EAE	$CCR2^{+}CD11b^{+}Ly6C^{+}$	Undetermined	May contribute to pathology	*King et al*
	EAE	blood $CD11b^{+}Ly6G^{-}$	Nitric Oxide (partial)	Not protective	*Slaney et al*
	TMEV infection	$CD11b^{+}Ly6C^{+}$	Undetermined	May contribute to pathology	*Bowen et al*
Inflammatory bowel disease	Villin-HA; adoptive transfer HA-specific T cells	$CD31^{+}CD11b^{+}Gr1^{+}$	Nitric Oxide - Apoptosis	Capable of suppressing autoimmune injury after adoptive transfer	*Haile et al*
Autoimmune hepatitis	BALB/c-*Tgfb1*$^{-/-}$	$CD11b^{+}Ly\text{-}6C^{high}Ly\text{-}6G^{-}$	Nitric Oxide	Not protective	*Cripps et al*; JG Cripps and JD Gorham, unpublished
Myasthenia gravis	EAMG	Not determined	Apoptosis	Not determined	*McIntosh & Drachman*
Inflammatory eye disease	EAU	$CD11b^{+}Gr1^{+}Ly6G^{-}$	Undetermined; TNFR-dependent	Not determined	*Kerr et al*
Systemic lupus erythematosus	MRL-*fas*^{lpr}	$CD11b^{+}Gr1^{low}$	Arginase	Not determined	*Iwata et al*
Alopecia areata	Alopecia areata-Eczema	$CD11b^{+}Gr1^{+}$	CD3-zeta down-regulation	Possibly protective: MDSC application to skin reduced AA	*Marhaba et al*
Type 1 Diabetes	INS-HA/*Rag*$^{-/-}$; adoptive transfer HA-specific $CD4^{+}$ T cells	$Gr1^{+}CD115^{+}$	Undetermined	Possibly protective: suppressed autoreactive T cells after adoptive transfer	*Yin et al*