derstanding of the impact of microenvironmental hypoxia in the context of chronic inflammation will open new windows of therapeutic potential in a wide range of inflammatory disease states.

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KEY WORDS:
hypoxia · inflammation · metabolism

Editorial: **The contribution of myeloid-derived suppression to inflammatory disease**

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RECEIVED APRIL 14, 2014; REVISED MAY 12, 2014; ACCEPTED MAY 25, 2014. DOI: 10.1189/jlb.3CE0414-205R

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Both innate and adaptive immune mechanisms exist to restrain inflammatory T lymphocyte responses and protect against excessive host damage. Aberrant activation of regulatory mechanisms, however, can lead to strong immunosuppression that is detrimental in infectious diseases and cancer. In the adaptive immune response, T_{regs} represent one such regulatory mechanism with well-defined markers and roles in restricting inflammation [1]. The characteristics exhibited by immunosuppressive cells of the innate immune response are not as clear. It has been known for a number of years that a heterogeneous population of $CD11b^+Gr1^+$ cells, collectively known as MDSCs, is associated with the repression of anti-tumor T cells. Likewise, MDSC-like cells are also expanded under inflammatory conditions, which may represent a relatively unexplored regulatory mechanism with the potential to influence the course and outcome of the immune response.

In mice, MDSCs can be generally classified as G-MDSCs ($CD11b^+Ly6G^+$) or M-MDSCs ($CD11b^+Ly6C^+$), with a variety of additional markers and suppressor mechanisms further subdividing the population (reviewed in ref. [2]). Both types of MDSC subsets are up-regulated in various cancers, where they have been shown to inhibit deleteriously T cell-dependent tumor immunity [2]. Although human and mouse MDSCs can use many different suppressive mechanisms, the predominant means are arginase 1 and iNOS enzymatic activity, which are important for L-arginine starvation and the inhibition of T cell signaling [2, 3]. Additionally, MDSCs have been implicated in inhibiting the activation of anti-tumorigenic cells, such as $CD8^+$ T cells and NK cells, while still using various cell-contact and soluble mechanisms to promote reciprocally antigen-specific activation and ex-

Abbreviations: cLP=colon lamina propria, DSS=dextran sulfate sodium, EAE=experimental autoimmune encephalomyelitis, G-MDSC=granulocytic myeloid-derived suppressor cell, IBD=inflammatory bowel disease, M-MDSC=monocytic myeloid-derived suppressor cell, MDSC=myeloid-derived suppressor cell, MLN=mesenteric lymph node, T_{reg}=regulatory $CD4^+$ T cell

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pansion of inducible T_{regs} [4]. MDSCs were also recently found to suppress further anti-tumor responses through the production of peroxynitrite, which interferes with the binding of tumor-specific antigens to MHC class I and results in evasion from $CD8^+$ T cell recognition [5].

G-MDSC and M-MDSC populations, similar to those observed in cancer, have also been described in inflammation and autoimmunity, although the importance of these cell types remains undetermined. Zhu et al. [6] demonstrated that splenic $CD11b^+$ cells are expanded following the induction of EAE and could be separated into different populations based on $Ly6G^{high}$ and $Ly6C^{high}$ expression. Nevertheless, only the splenic $Ly6C^{high}$ population was capable of inhibiting T cell proliferation. The MDSCs induced during the EAE model were phenotypically similar to M-MDSCs; however, only iNOS activity was important for inducing T cell apoptosis, whereas arginase 1 was dispensable. In the CNS tissue, MDSC-like cells made up a large component of the infiltrate at the height of the disease, although the suppressive activity of the infiltrating cells was not investigated. Conversely, another study provided evidence that the G-MDSC ($Ly6G^{high}$) subset is expanded as well, following the induction of EAE [7]. The suppressive mechanism in this case is different compared with M-MDSC, in that Th17 responses were inhibited through programmed death ligand 1 expression on G-MDSC rather than iNOS or arginase 1 activity [7]. Thus, innate expansion and suppressor mechanisms are highly heterogeneous and likely depend on the nature of inflammation.

MDSCs are enriched during colon inflammation and cancer as well. Recent work has demonstrated that CXCR2 expression by G-MDSCs during chronic inflammation is critical for the entry of these cells into the colonic mucosa, were they promote tumor growth through the suppression of anti-tumor T cell responses [8]. Importantly, this work has implications for targeting MDSCs in cancer therapy through inhibiting migration into the affected tissue rather than expansion or activation. Other research has shown that M-MDSCs, rather than G-MDSCs, are recruited during IBD models of chronic colon inflammation. Haile et al. [9] found that the $CD11b^+Gr1^+$ population is expanded in the spleen following the onset of $CD8^+$ T cell transfer colitis. Within the $Gr1^+$ population, Ly6C was the dominant marker on the cells that had potent T cell-suppressive activity. These M-MDSCs also exhibited high expression of iNOS and arginase 1, and cotransfer of the splenic MDSC population could ameliorate colitis induction and severity. Importantly, PBMCs isolated from human IBD patients showed a similar expansion of cells with human MDSC markers. In this issue of the *Journal of Leukocyte Biology*, Kurmaeva et al. [10] characterize in detail a similar population of $CD11b^+Ly6G^-Ly6C^+$ Dectin-1^+ cells (termed $Ly6C^{high}$) that increases in circulation following the induction of colitis. This work expands upon their previous research, describing in detail the sizable myelopoiesis that accompanies the development of chronic colitis [11]. Interestingly, in addition to blood and spleen, the authors found that this population was enriched in the intestinal MLN and cLP in a model of $CD4^+CD45RB$ T cell transfer colitis. Unlike previous studies, the authors tracked the kinetics of monocytic invasion in the cLP for 7 weeks and found that this population was still highly infiltrated in the mucosa at the late stages of disease. Overall, these findings expand on previous work to demonstrate that chronic colon inflammation is characterized by a constant MDSC infiltration.

As mentioned for cancer, MDSCs use a combination of mechanisms to exert their suppressive activity on T cells; the best characterized are iNOS and arginase 1 activity. However, the suppressive mechanism for M-MDSCs, induced during inflammation, seems to involve only iNOS, where inhibition of NO production abrogates their suppressive activity [6, 9, 10]. Many of the studies that have investigated MDSC activity in inflammatory models are primarily examining populations isolated from the periphery. Considering that MDSCs are a heterogeneous population [2], one must ask whether there exists a difference between the phenotype of $Ly6C^{high}$ cells isolated from the spleen compared with the site of inflammation. Furthermore, keeping the MDSC out of the affected tissue rather than the periphery seems to be a more effective strategy to inhibit tumor development and progression [8]. This question was addressed in the current study, where the authors compared the morphology, surface-marker expression, and suppressive activity of $Ly6C^{high}$ cells isolated from the spleen and the cLP [10]. Whereas MDSCs isolated from both locations were able to inhibit $CD4^+$ T cell proliferation, the suppressive mechanisms involved were slightly different. Splenic $Ly6C^{high}$ cells needed iNOS and IFN-γ, whereas colonic $Ly6C^{high}$ cells relied on NO production and cell-to-cell contact. $Ly6C^{high}$ cells, isolated from the colon, were morphologically distinct and expressed higher levels of iNOS and arginase 1, as well as having stronger suppressor function compared with those found in the spleen. Therefore, different inflammatory conditions coupled with different localization may determine the nature and effectiveness of the myeloid-suppressor population (**Fig. 1**). The initial expansion of MDSC-like cells observed at the onset of EAE is somewhat contradictory, as severe inflammation still does occur [6, 7]. Thus, the MDSC population that develops in the early stages of inflammation in the periphery may function differently (proinflammatory vs. suppressive roles) from those isolated at the site of inflammation at the later stages of disease. This is supported in the highlighted study, where $Ly6C^{high}$ cells, isolated from the colon, were the most potent subset of suppressive MDSCs [10].

MDSCs are clearly involved in specific models of colon inflammation; however, it remains to be determined if these are a universally induced population. Expansion of MDSC relies heavily on STAT3 activation [2], so the increase in soluble mediator production observed during inflammation may expand MDSC in a global manner, independent of the inflammation location. An argument can be made that in all T cell-dependent models of chronic colitis, the cytokine environment is quite favorable for the expansion and activation of MDSC. But, what about colitis models

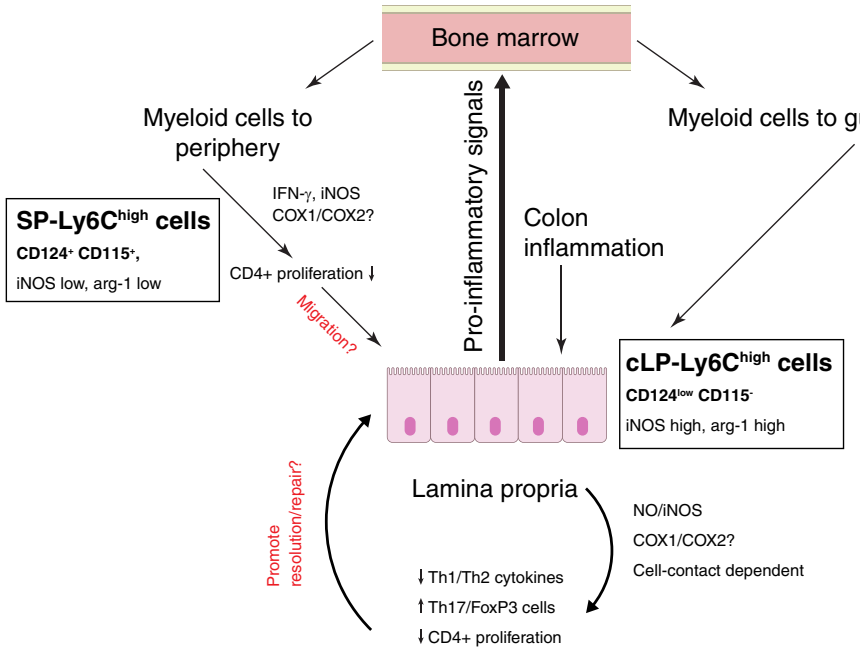


Figure 1. Mechanisms of immunosuppression by Ly6C^{high} cells in a colitis model. Proinflammatory mediators induced during colitis development signal for myelopoiesis, trafficking, and activation of myeloid cells in the bone marrow, periphery, and colon. These differentiate into various cell types, including M-MDSCs, which are characterized by Ly6C^{high} expression. Ly6C^{high} cells are divided further into subsets with different morphologies, depending on whether they reside in the spleen (SP- Ly6C^{high} CD124^{+} CD115^{+}) or colon (cLP-Ly6C^{high} CD124^{low} CD115^{-}). Whereas both have immunosuppressive properties, the mechanisms are slightly different, with the cLP Ly6C^{high} cells as the more potent immunosuppressors. COX1/2, Cyclooxygenase 1/2; arg-1, arginase 1; FoxP3, forkhead box P3.

that are acute or develop independently of T cells? Previous work provides conflicting results with the highlighted report regarding DSS-induced colitis [9]. With the use of a chronic model of DSS-induced intestinal inflammation, the authors show that after 33 days, there was no difference in the number of CD11b^{+}Gr1^{+} cells in the spleen or MLN compared with healthy control animals. In contrast, the current study reveals that at Day 7 post-DSS administration, a similar expansion of Ly6C^{high} cells is observed in the spleen and cLP. Whether the cells in the acute DSS model were as suppressive as those observed in chronic T cell transfer models remains undetermined, but the presence of these cells in an acute model suggests that the innate mediators invoked during the initial barrier breakage may provide sufficient feedback for the expansion of additional innate monocytic cells, including MDSCs, which are responsible for restraining inflammation and promoting repair responses (Fig. 1).

MDSCs are readily found, albeit in a heterogeneous manner, during inflammatory disorders in humans and mice. However, aberrant activation of inflammatory T cell responses still occurs in disease, despite the presence of expanded and activated MDSC populations. Therefore, MDSCs likely represent just a component of the protective mechanisms that exist to protect against unrestrained inflammation. Whereas the effect of MDSC inhibition on T cell responses in vitro may be potent, the suppressive activity of these cells in vivo is likely dampened by the milieu of additional mediators and cellular populations coexisting in the same inflammatory microenvironment. Furthermore, the MDSCs that are expanded in the previously described murine inflammatory models lack some of the suppressive mechanisms, namely arginase 1, that have been described for the seemingly more vigorous MDSCs that are found in cancer models and patients. Consequently, the MDSCs involved in inflammation may be playing additional roles outside of broadly inhibiting all inflammatory T cell responses. Supportive evidence for this comes from the current manuscript, where the authors demonstrated that the Ly6C^{high} cells in the colon are powerful inhibitors of Th1 responses. However, Ly6C^{high} cultures also contained elevated IL-1β and IL-6 protein, which subsequently promoted Th17 generation in the absence of IFN-γ, whereas not substantially affecting the expansion of T_{regs} [10]. Moreover, Th17 cells and IL-17 production are elevated in murine and human IBD [12, 13]. Thus, in models of inflammation, MDSCs with various suppressive mechanisms are induced, depending on the nature of inflammation, where they may serve to restrain T cell proliferation with direct or indirect consequences to specific subsets of inflammatory T cells. More specifically, the recruitment and activation of MDSCs during intestinal inflammation may precede the development of Th17-biased immune responses and represent a permissive rather than suppressive mechanism for Th17 generation. In that regard, future therapeutics involving the treatment of inflammatory disorders with expanded MDSCs seem promising, but further research is needed to characterize fully the various effects that MDSCs have on all of the components of the immune response.

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KEY WORDS:

MDSC · IBD · colon inflammation · cancer