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EDITORIAL

Is Avoiding Stem Cell Exhaustion the New Therapeutic Approach in Colitis?

Hematopoietic stem cells (HSCs) are pluripotent cells with the capacity for self-renewal.[1] They comprise about 0.01% of bone marrow cells and are localized to stem cell niches in the endosteum and perivascular region where regulation of their proliferation, differentiation, and bone marrow retention is provided by critical signals from stromal cells. Inflammation stimulates increased production of immune effector cells. In comparison to progenitor cells, HSCs at baseline are quiescent or dormant, with most long-term HSCs in the G0 cell cycle phase.[2] This dormant state is characterized by limited divisions and is critical to preservation of the self-renewal, repopulating capacity of HSCs needed for prevention of "exhaustion."[3]

Although mature myeloid cells traffic to the gut in acute inflammatory states to promote intestinal repair or fight infection (eg, macrophages play a critical role in the intestinal regenerative response to injury),[4] the regulation and contribution of HSCs responsible for production of these effector cells in intestinal inflammation are less understood. Moreover, the short-term output of immune effector cells and acute myeloid demand need to be balanced with the potential for HSC exhaustion and depletion. Prior elegant work from the Wang lab has shown that myeloid-biased HSCs (MB-HSCs) are a lineage-specified subcompartment of a heterogeneous adult HSC population, accounting for around 0.002% of total bone marrow nucleated cells. Quiescent MB-HSCs and myeloid progenitors are marked by the histamine-synthesizing enzyme, histidine decarboxylase (HDC). Of the 4 histamine receptors (H1R, H2R, H3R, and H4R**),** only H2R is detectable on MB-HSCs and progenitors. HDC+ MB-HSCs reside within a cluster of mature HDC-expressing, histamine-producing myeloid cells needed to promote the quiescence and self-renewal of MB-HSCs via activation of H2R. Increased myeloid demand in response to lipopolysaccharide treatment leads to recruitment of MB-HSCs into the cell cycle depletion, inability to revert to quiescence, and eventual depletion. Conversely, an H2 agonist protects MB-HSCs from depletion after sepsis.[5] Thus, in addition to traditional stromal cells, lineage HDC+ myeloid cells daughter cells are a niche component that sustains the dormancy of MB-HSCs.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Fu et al[6] from the Wang laboratory sought to explore the role of HDC-expressing myeloid cells and MB-HSCs in the setting of acute colitis by using the dextran sulfate sodium (DSS)-induced intestinal injury model of inflammatory bowel disease. Although the mechanism by which DSS induces intestinal inflammation is not entirely clear, it is likely the result of epithelial damage of the lining of the large intestine that allows infiltration of proinflammatory luminal contents such as bacteria and their products into underlying mucosa and subsequent activation of the innate immune system.[7]

Using previously described HDC–green fluorescent protein (GFP) transgenic mice treated with DSS, they first show a decrease in the percentage and number of bone marrow HDC+ MB-HSCs in the bone marrow that correlated with worse histologic scores. The loss in bone marrow HDC + HSCs was coupled with an increase in MPP3, suggesting HDC + HSC activation and further differentiation. In turn, using fluorescent-activated cell sorter and cell cycle analysis, they showed loss of MB-HSC quiescence with exit from the G0 phase of the cell cycle. In concert with these findings, the number of HDC+ myeloid cells was diminished in the bone marrow along with an increase in circulation of HDC+ myeloid cells and an infiltration of HDC+ myeloid cells into the colon during DSS colitis. These findings demonstrate that in DSS colitis, MB-HSC depletion occurs in the setting of decrease of HDC+ myeloid cells, the population of niche cells primarily responsible for histamine production in the bone marrow. Because they had previously shown that histamine is necessary to prevent activation of MB-HSCs from their quiescent/dormant state, this observation raises the possibility that the progressive decline in the number of functional MB-HSCs or exhaustion may be involved in pathogenesis of DSS colitis.

To further demonstrate the role of histamine, they began with HDC knockout mice lacking HDC gene expression. In the DSS-treated HDC knockout mice, the HDC+ MB-HSC population decreased in the bone marrow, with a lower percentage in the quiescent G0 phase and a greater percentage of proliferating cells vs DSS-treated HDC-GFP mice. In concert, GFP+ myeloid cells in the bone marrow, circulation, spleen, and colon of DSS-treated HDC-deficient mice increased compared with DSS-treated HDC-GFP mice. Severity of colitis and survival were worse in the knockout mice. These findings show that the loss of the inhibitory break normally conferred by HDC derived histamine leads to greater depletion and activation of HDC+ MB-HSCs and greater colonic recruitment of HDC+ myeloid cells, with worse colitis and survival in response to DSS.

Then, using HDCCreERT-inducible diphtheria toxin receptor (DTR) mice to deplete HDC+ myeloid cells, they were able to test more directly the role of these niche cells in maintaining HDC+ MB-HSC quiescence during colitis. Similar to the HDC knockout mice, HDC+ myeloid cell depletion led to a bone marrow decrease in the number of HDC+ MB-HSCs, a lower percentage in a quiescent G0, and an increase in the percentage that were bromodeoxyuridine positive compared with DSS-treated HDC-GFP mice. In addition, the DT-treated DTR+ mice showed a decrease in body weight compared with DTR– mice and worse overall survival, albeit without significant changes in histologic assessment and scoring. Thus, depletion of the daughter niche cells HDC+ myeloid cells led to MB-HSC depletion, activation, and overall worse survival.

Finally, because loss of quiescence of MB-HSCs either via knockout of the HDC gene or depletion of HDC+ myeloid cells led to worse survival, they used a specific H2R agonist dimaprit dihydrochloride to test the therapeutic benefit of promoting quiescence. Although histologic severity was similar at the end of the DSS treatment, overall body weight loss was less severe and survival was improved in the H2R agonist treatment group. Importantly, the number of bone marrow HDC+ MB-HSCs increased, a higher percentage were in the quiescent GO phase compared with untreated mice, and there was a lower percentage of bromodeoxyuridine-positive HDC+ MB-HSCs. The number of bone marrow HDC+ myeloid cells increased, whereas colonic infiltration of HDC+ myeloid cells was decreased without a change in the monocyte or macrophage population of the spleen. Concurrently there were decreases in interleukin 6 and granulocyte-macrophage colony-stimulating factor, which are involved in regulation of HSC proliferation and differentiation. Overall, these findings suggest that improved survival is mediated by preventing MB-HSC exhaustion.

The data from this straightforward, well-designed study are an expansion of prior studies in the Wang lab on the regulation of MB-HSCs in the setting of infectious and inflammatory stress.[5] Their work now supports the important role of HDC-derived histamine and H2R in modulating the response to severe acute intestinal inflammation in an acute model of DSS colitis. Interestingly, an increase in mucosal histamine has been previously shown in animal models of inflammatory bowel disease (IBD). In addition, modulation of H4R has been investigated, and antagonism of the H2R has shown some benefit in the DSS model and in IBD patients.[8-11] However, as correctly pointed out by the Wang group and others,[12,13] the results of these studies are rife with heterogeneity and inconsistency that are contributed in part by the use of different models of murine IBD and a focus on the mucosal effect on colitis rather than on a HSC system responsible for providing mucosal immune cells integral to the injury/repair process.

Importantly, this study expands our understanding of the pathogenesis of DSS colitis beyond the current conception of a colitis characterized by mucosal injury and innate immune responses to highlighting the interaction between the bone marrow and colon in the context of acute myeloid demand and MB-HSC exhaustion. Investigation of the histamine/H2R axis is certainly needed in chronic and other models of colitis. Although HSC transplant has been applied/studied in clinical trials for medical refractory IBD, primarily Crohn's disease, endpoints are not well-defined, and adverse events including infections have been reported.[14] As such, the translational potential of studies by this group brings us a step closer to developing a new avenue of stem cell therapeutics not currently addressed by available therapies.

ANISA SHAKER, MD
Department of Medicine
Division of Gastroenterology and Hepatology
University of Southern California Keck School of Medicine
Los Angeles, California

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Correspondence
Address correspondence to: Anisa Shaker, MD, Department of Medicine, Division of Gastroenterology and Hepatology, University of Southern California Keck School of Medicine, 2011 Zonal Avenue, HMR 810, Los Angeles, California 90089. e-mail: ashaker@usc.edu.

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