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EDITORIAL

Granulocyte-Macrophage Colony-Stimulating Factor-Activated Monocytes as an Anti-inflammatory Player in the Intestine

In the present issue of *Cellular and Molecular Gastroenterology and Hepatology,* Weinhage et al[1] report on how granulocyte-macrophage colony-stimulating factor (GM-CSF)-activated monocytes can modulate the severity of intestinal inflammation, as shown using various mouse models of chronic colitis. As the authors point out, blood monocytes are the source of macrophages and dendritic cells (DCs) in the intestinal mucosa, and were previously reported to play key roles in the pathogenesis of Crohn's disease.[2,3] Based on this, any therapeutic approach aimed at modulating this key player in innate immunity could be a potent way to modulate/manage intestinal inflammation in patients with chronic intestinal inflammation.

For example, the cytokines macrophage colony-stimulating factor and GM-CSF promote the differentiation of monocytes into macrophages and DCs.[4,5] Moreover, investigations in a mouse model of colitis induced by dextran sulfate sodium (DSS) have shown that GM-CSF can partially protect against intestinal inflammation, and that GM-CSF-deficient mice show increased susceptibility to DSS-induced colitis.[5,6] Injection of DSS-colitis mice with GM-CSF was shown to trigger the accumulation of splenic $CD11b^+$ cells, which promote wound healing and epithelial cell proliferation and thereby reduce disease severity. More importantly, GM-CSF was found to promote clinical responses in patients with active Crohn's disease. However, the full action mechanism of GM-CSF, and especially whether monocytes mediate its effects in vivo, had not been previously elucidated.

In their elegant study, Weinhage et al[1] activated bone-marrow-derived monocytes with GM-CSF in vitro. After this GM-CSF treatment, the monocytes were found to overexpress some surface markers of specialized macrophages (eg, CD39, CD73, and CD121b) and some stimulatory molecules (eg, CD80, CD86, MHCII, and B7-H1) while showing decreased expression of a marker for alternatively activated monocytes (fractalkine receptor CX3CR1). In addition, the authors noted discrepancies in the expression levels of some M2-polarized markers. Because this expression profile did not fully recapitulate the previously reported activation stages of monocytes, the authors proposed that the newly generated monocytes represented a unique and distinct state of activation. These GM-CSF-activated monocytes (GMaMs) were also found to be somewhat unique from a functional point of view. The authors demonstrated in vitro that this population has a lower capacity for phagocytosis and adhesion, but triggers increased generation of reactive oxygen species, which are required for pathogen clearance. Moreover, after lipopolysaccharide treatment, proinflammatory cytokine production was found to be higher in GMaMs compared with untreated monocytes.

The authors then tested these GMaMs on the DSS-induced mouse model of chronic colitis. Importantly, GMaM-treated mice showed clear improvements in intestinal inflammation and lower proinflammatory cytokine expression levels in the distal colon. The authors next sought to decipher the mechanism by which GMaMs confer their therapeutic effects on intestinal inflammation. They showed that, compared with control monocytes, the GMaMs were taken up faster by the intestine and stayed there longer, especially in the Peyer's patches.

In addition to these unique migratory features, the GMaMs increased the accumulation of forkhead box P3 positive ($Foxp3^+$) T cells in the lymph follicles when compared with untreated mice or those treated with nonactivated monocytes. Importantly, this GMaM-mediated protection was completely abolished in $Rag1^{-}/^{-}$ mice (which lack all mature adaptive immune cells). Injection of GMaM was not able to protect the mice against DSS-induced colitis, indicating that adaptive immunity is required for the GMaM-mediated protection against colitis. Furthermore, after T-cell transfer into $Rag1^{-}/^{-}$ mice (another model of chronic colitis; fully T-cell dependent), subsequent injection of GMaMs had beneficial effects on colitis and increased the $Foxp3^+$ $CD4^+$ T-cell population. In an in vitro model in which GMaMs were cocultured with naive T cells, the authors observed increased proliferation and differentiation of $Foxp3^+$ regulatory T cells (Treg) and found that this occurred through a mechanism that involves the CD39-mediated conversion of ATP into adenosine (a mechanism that was previously reported to induce Treg cell differentiation).

Taken together, these important data show that GM-CSF activates GMaMs, a specific population of monocytes that has a protective effect against intestinal inflammation. The beneficial effects of GMaMs are T-cell dependent and involve the CD39/adenosine-mediated proliferation and differentiation of $Foxp3^+$ Treg cells.

EMILIE VIENNOIS
Institute for Biomedical Sciences
Center for Diagnostics and Therapeutics
Georgia State University
Atlanta, Georgia

DIDIER MERLIN
Institute for Biomedical Sciences
Center for Diagnostics and Therapeutics
Georgia State University
Atlanta, Georgia

Atlanta Veterans Affairs Medical Center
Decatur, Georgia

References

1. Weinhage T, Däbritz J, Brockhausen A, et al. Granulocyte Macrophage Colony-Stimulating Factor–Activated $CD39^{+}/CD73^{+}$ Murine Monocytes Modulate Intestinal Inflammation via Induction of Regulatory T Cells. Cell Mol Gastroenterol Hepatol 2015;1:433–449.
2. Zhou L, Braat H, Faber KN, et al. Monocytes and their pathophysiological role in Crohn's disease. Cell Mol Life Sci 2009;66:192–202.
3. Dabritz J. Granulocyte macrophage colony-stimulating factor and the intestinal innate immune cell homeostasis in Crohn's disease. Am J Physiol Gastrointest Liver Physiol 2014;306:G455–G465.
4. Sweet MJ, Hume DA. CSF-1 as a regulator of macrophage activation and immune responses. Arch Immunol Ther Exp (Warsz) 2003;51:169–177.
5. Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. Nat Rev Immunol 2008;8:533–544.
6. Xu Y, Hunt NH, Bao S. The role of granulocyte macrophage-colony-stimulating factor in acute intestinal inflammation. Cell Res 2008;18:1220–1229.

Correspondence
Address correspondence to: Emilie Viennois, PhD, Institute for Biomedical Sciences, Georgia State University, Atlanta, Georgia 30303. e-mail: eviennois@gsu.edu.

Conflicts of interest
The authors disclose no conflicts.

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