# Granulocyte-Macrophage Colony Stimulating Factor and Inflammatory Bowel Disease: Establishing a Connection

**See "Defective leukocyte GM-CSF receptor (CD116) expression and function in inflammatory bowel disease," by Goldstein JI, Kominsky DJ, Jacobson N, et al, on page 208.**

In clinical oncology, the recognition that tumors of shared morphology and presentation may encompass distinct subsets driven by alternative mechanisms has ushered in a new era of personalized cancer medicine.[1] For example, subtypes of lung adenocarcinomas that are characterized by activating mutations in the epidermal growth factor receptor or the anaplastic lymphoma kinase may show dramatic responses to specific agents targeting these proteins, whereas other seemingly related lung tumors will likely prove refractory. Similarly, malignant melanomas that harbor gain-of-function alterations in B-Raf or c-Kit may be sensitive to small molecule inhibitors of these kinases, while apparently comparable tumors without such genetic profiles will largely be resistant.

Advances in understanding the pathogenesis of inflammatory bowel disease (IBD) are likely to yield an analogous paradigm of personalized care. Although IBD is typically divided into ulcerative colitis and Crohn's disease based on clinical and pathologic features, substantial heterogeneity is evident within this classification.[2] Genome-wide population studies have uncovered a large number of IBD susceptibility loci, but individually these account for only small proportions of affected patients. The genetic complexity is compounded further by significant variations in gut microbiota and environmental exposures, which together create myriad pathways that culminate in unresolved intestinal inflammation.

Notwithstanding this heterogeneity, elegant clinical investigations of Crohn's disease patients suggest that defects in acute inflammation might be a unifying feature.[3] The experimental induction of trauma to the rectum, ileum, or skin of patients triggers less neutrophil recruitment, diminished levels of interleukin (IL)-1$\beta$ and IL-8, and decreased blood flow compared to healthy controls. These compromised reactions impede the clearance of killed *Escherichia coli* inoculated into the skin. Moreover, macrophages from Crohn's disease patients release lower levels of pro-inflammatory cytokines after Toll-like receptor stimulation, reflecting an alteration in protein trafficking that favors lysosomal proteolysis over secretion.[4] These results suggest that functional abnormalities in neutrophils and macrophages may compromise mucosal immunity, thereby facilitating breach of the epithelial barrier by luminal bacteria.

Based on the therapeutic activity of colony stimulating factors in congenital phagocyte disorders, clinical trials of recombinant granulocyte-macrophage colony stimulating factor (GM-CSF) were undertaken in Crohn's disease.[5–8] Several small studies intimated that some patients benefit from cytokine administration, with reductions in disease severity and corticosteroid requirements. Larger, randomized trials failed to achieve primary clinical end points, though, raising uncertainty regarding the overall efficacy of GM-CSF. Although the basis for these discordant results remains to be clarified, one possibility, suggested by analogy with the concept of personalized medicine in oncology, is that only a subset of Crohn's disease subjects responds to GM-CSF. In this issue of GASTROENTEROLOGY, Colgan et al[9] begin addressing this idea by characterizing the expression of CD116, a component of the GM-CSF receptor, on circulating granulocytes and monocytes from IBD patients.

The GM-CSF receptor is a heterodimer composed of a unique alpha chain (CD116) that binds the cytokine with low affinity, and a shared (with the receptors for IL-3 and IL-5) beta chain that interacts with both the alpha chain and GM-CSF to accomplish high-affinity binding.[10] The crystal structure revealed a dodecamer or higher-order complex, in which 2 beta chains contained within separate hexamers are brought into close apposition. This architecture facilitates the trans-phosphorylation of associated JAK-2 molecules upon cytokine stimulation, thereby propagating signals through the STAT-5, MAP kinase, and PI-3 kinase pathways. This receptor organization permits also graded cellular responses dependent on cytokine concentration, which may account in part for the pleiotropic effects of GM-CSF on myeloid cell survival, proliferation, differentiation, and function.[11]

Colgan et al[9] observed decreased CD116 expression on granulocytes and monocytes from both Crohn's disease and ulcerative colitis patients, as compared with healthy donors and subjects with irritable bowel syndrome or rheumatoid arthritis. CD116 mRNA and protein levels were coordinately diminished, suggesting that transcriptional mechanisms might underlie the decrease, rather than increased membrane shedding of soluble receptor isoforms. GM-CSF induced signaling, as assessed by STAT-3 phosphorylation, was correspondingly reduced. Disease status and concurrent medications did not influence expression levels. Because the receptors for the closely related cytokines G-CSF and IL-3 were intact, some specificity for CD116 was established, although future investigations should also characterize beta chain expression.

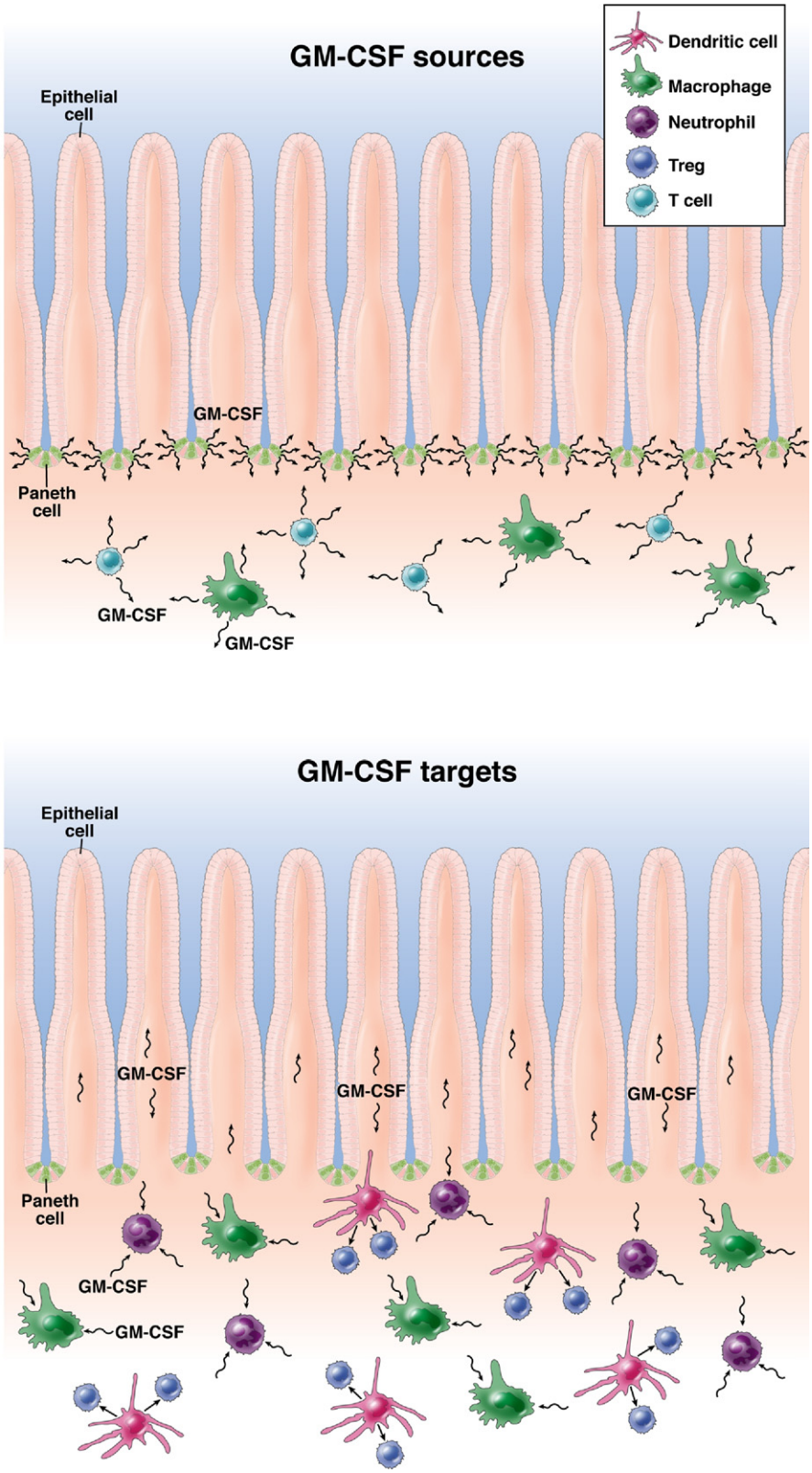


**Figure 1.** GM-CSF contributes to intestinal homeostasis through multiple mechanisms. Paneth cells and hematopoietic elements may secrete GM-CSF. The cytokine may act on epithelial cells to modulate proliferation and survival. GM-CSF is required for $CD103^+$ dendritic cells, which support the generation of regulatory T cells. GM-CSF modulates the activities of macrophages, which may contribute to control of the inflammatory response and mucosal repair. Neutrophils require GM-CSF for optimal function during infection and injury.

These intriguing findings raise the possibility that alterations in GM-CSF function might be linked to some cases of IBD. In accordance with this idea, a subset of pediatric and adult patients with Crohn's disease, particularly those with ileal involvement and stricturing/penetrating pathology, were shown previously to develop neutraliz-