Selective advantage of inflammation anergy in gut macrophages

In 1985, Simon Gordon and colleagues[1] demonstrated that the largest reservoir of macrophages in the mouse (and by extrapolation the human) is the lamina propria of the small and large intestine. For the next 10 years, lamina propria macrophages were assumed to function like macrophages in other tissues, directing the response to immunostimulatory microorganisms through an array of receptors such as CD14, the receptor for complexes of lipopolysaccharide (LPS) and LPS-binding protein, and the release of proinflammatory mediators. This assumption began its slow erosion during the 1990s, when macrophages in normal human colonic and intestinal mucosa were first shown to lack CD14, whereas up to 25% of mucosal macrophages in patients with inflammatory bowel disease (IBD) expressed CD14. To determine the origin of these $CD14^+$ macrophages, Grimm and colleagues[2] elegantly showed that autologous $CD14^+$ blood monocytes labeled with ^{99m}technetium and then inoculated back into subjects with IBD recruited to the inflamed mucosa, confirming that the $CD14^+$ macrophages in the inflammatory lesions were newly recruited proinflammatory blood monocytes. In connection with this, a recently described[3] subset of macrophages isolated from the colon (not the small intestine) of patients with IBD that expressed CD14 and released proinflammatory cytokines probably represents newly recruited blood monocytes.

To define the contribution of mucosal macrophages to IBD- and infection-associated gut inflammation, we[4,5] and Schenk and colleagues[6,7] have begun to elucidate the immunobiology of resident macrophages in the normal human small intestine. In noninflamed intestinal mucosa, macrophages are profoundly downregulated for an array of innate response receptors, including the receptors for LPS, immunoglobulin A (IgA), and IgG; triggering receptor expressed on myeloid cells-1; activation markers (CD25, CD40, CD80, and CD86) (refs. 4–7); and, as we recently reported,[8] the chemokine coreceptors CCR5 and CXCR4. Moreover, intestinal macrophages are profoundly downregulated for inducible production of proinflammatory (interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-α) and regulatory (IL-10, IL-12, and transforming growth factor-β (TGF-β)) cytokines, a condition we have termed "inflammation anergy."[5] Notably, human intestinal macrophages do not produce IL-10, in sharp contrast with murine colonic macrophages, which are capable of inducible IL-10 release.[9] Despite this profound inflammation anergy, intestinal macrophages retain host defense activities through avid phagocytic and bacteriocidal function, enabling the cells to rapidly eliminate bacteria that penetrate the epithelium without promoting local inflammation.[4]

How do intestinal macrophages become non-inflammatory? In addressing this question, we have shown that proinflammatory blood monocytes chemotax to TGF-β and IL-8 derived from intestinal mast cells and epithelial cells and that blood monocytes are the exclusive source of intestinal macrophages.[10] Underscoring the role of the extracellular matrix in mucosal immunobiology, extracellular matrix (stroma)-associated TGF-β, and possibly other associated factors, then induces the differentiation of the newly recruited proinflammatory blood monocytes into noninflammatory intestinal macrophages.[4] However, ineffective downregulation of intestinal macrophage phenotype and function may contribute to retained proinflammatory capabilities in monocytes newly recruited to the mucosa in patients with IBD. Recent intriguing studies from our laboratory indicate that the mechanism of the inflammation anergy in resident lamina propria macrophages involves stromal TGF-β-mediated dysregulation of nuclear factor-κB (NF-κB) signal proteins and constitutive Smad-induced IκBα production in the cells (Smythies *et al.*, manuscript submitted). The extracellular matrix of the intestinal lamina propria (and perhaps other mucosal compartments) appears to induce a phenotype and functional profile that is unique among tissue macrophages. For example, intestinal macrophages also lack the chemokine coreceptors CCR5 and CXCR4 that mediate HIV-1 entry and do not support HIV-1 replication (an NF-κB-dependent process), whereas genital (vaginal) macrophages express these receptors and support replication by both CCR5- and CXCR4-tropic HIV-1 (ref. 8).

What could possibly be the advantage of noninflammatory intestinal macrophages, and how might they have evolved? In the gastrointestinal tract mucosa, macrophages are located exclusively in the lamina propria, where they are strategically positioned for close proximity to lumenal microorganisms. For millions of years, an astonishingly unhygienic environment presented the evolving intestine of early vertebrates, then nonhuman primates, and eventually humans, with a spectrum of microbiota and infectious pathogens likely far greater in complexity and numbers than that of today. In such an environment, a disrupted intestinal epithelium due to frequent infections was likely common. Responding to this formidable immunostimulatory challenge, the gut intestine coevolved a mechanism to downregulate inflammatory, but not host defense, responses to lumenal microorganisms that breach the disrupted epithelium. Consequently, a resident lamina propria macrophage emerged that—at least in humans—is unique among tissue mononuclear phagocytes for its capacity to phagocytose and digest without mounting an inflammatory response. Extended to immune surveillance, our preliminary findings indicate that intestinal macrophages, like tissue macrophages from other sites, scavenge

apoptotic cells without inducing the release of proinflammatory cytokines. An inflammatory response to such innate activities would have been a selective disadvantage to the species during the development of the intestine. Today, the unique phenotype and functional profile of the intestinal macrophage contribute to the absence of mucosal inflammation in the small intestine, despite a "cleaner" microbiota. Further dissecting the cascade of interacting regulatory pathways in the induction of inflammation anergy will better equip us to understand the role of macrophages in IBD- and infection-associated mucosal inflammation.

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