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EDITORIAL

Here to Heal: Mucosal CD74 Signaling in Colitis

Inflammatory bowel disease (IBD) is characterized by chronic and relapsing intestinal inflammation resulting in significant morbidity and long-term complications. Mucosal healing predicts positive clinical outcomes and sustained remission in IBD patients, and has emerged as an endpoint for clinical trials and patient management. However, a significant subset of patients with IBD do not meet mucosal healing criteria or respond to current therapies, including biologics targeting immune cell factors such as tumor necrosis factor inhibitors and anti-integrins, underscoring a need for additional therapeutic options. To address this, a large number of ongoing clinical trials are evaluating new candidate drugs, including the recombinant fusion protein UTTR1147A targeting intestinal epithelial interleukin-22 receptors to promote mucosal repair. Promising results from a phase I clinical study showed improved clinical and pharmacodynamic responses in patients with ulcerative colitis treated with UTTR1147A compared with placebo.[1] Despite this progress, detailed molecular mechanisms driving mucosal repair responses in intestinal epithelial cells during inflammation still are under investigation. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Farr et al[2] report on a novel role for intestinal epithelial cell CD74 receptors in cell proliferation and wound healing during colitis that may yield future options to promote mucosal healing in patients with intestinal inflammation and IBD.

CD74 was first known for its role in antigen presentation. Subsequently, it was discovered as a receptor for the inflammatory cytokine macrophage migration factor (MIF), which is released by a variety of cell types during active inflammation. In immune cells, CD74 signaling is associated with cell proliferative, migratory, and survival functions facilitating the immune response.[3] Aside from a previous report showing up-regulation of CD74 expression in the inflamed colons of IBD patients,[4] relatively nothing is known regarding CD74 functions specific to IBD. Here, Farr et al[2] confirmed this finding of increased colonic CD74 in mucosal biopsy specimens from IBD patients, and remarkably show that inflammation results in strong de novo CD74 messenger RNA and protein expression in intestinal epithelial cells of patients with IBD and amebic colitis, as well as in multiple mouse recovery models of colitis. A role for epithelial cell CD74 in IBD is supported further by a recent report showing CD74 is up-regulated specifically on goblet cells in the intestinal epithelium.[5] Importantly, Farr et al[2] showed that mice lacking CD74 are unable to recover from acute colitis and attributed this finding to reduced protein kinase B (Akt) and extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation in cells lacking CD74 after MIF stimulation, leading to impaired proliferative and migratory signals in the epithelium. Thus, these findings suggest that agonists of epithelial CD74 could be used therapeutically to limit inflammation and enhance mucosal healing in intestinal inflammation and IBD.

Previous evidence has suggested a proinflammatory role for MIF/CD74-receptor signaling in the intestine, including studies showing that MIF knockout mice were protected from the onset of colitis.[6] However, data from in vivo wound healing studies performed on skin lesions in rats showed that MIF levels were significantly increased after skin injury and contribute to proliferation and migration of keratinocytes from the wound edge,[7] suggesting a key role for MIF in wound repair. Interestingly, dual roles for ligand-receptor complexes are becoming increasingly evident in the context of active inflammation and mucosal repair, challenging pre-existing definitions of proinflammatory and anti-inflammatory actions during inflammation (eg, the cytokine receptor interleukin-22R, and neuropeptide receptors CRHR2 and NK1R).

Collectively, the data presented by Farr et al[2] support a role for epithelial CD74-receptor signaling in the initiation of mucosal proliferative and wound healing responses, however, additional studies are needed to confirm the role of epithelial CD74 and fully exclude potential contributions by CD74-receptor activation on other cell types, including immune cells. In addition, it will be important to investigate the possibility of CD44 and/or other potential co-receptors as members of a CD74 complex in intestinal epithelial cells that could contribute to cell type–specific responses, given the inflammatory response of immune cell–derived CD74 signaling. Furthermore, although a key strength of this study was the inclusion and immunohistochemical analysis of tissues from human colitis and IBD, the findings presented reflect a relatively small sample size and should be validated in larger cohorts of patients with well-characterized disease. Finally, future in vivo studies could explore the prospect of combination therapies targeting both immune cell factors (eg, biologics) and intestinal epithelial cell CD74 signaling on epithelial cell proliferation, migration, as well as other cellular responses contributing to the overall process of mucosal repair such as apoptosis and goblet cell differentiation.

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