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EDITORIAL

A Cellular "Hub" Function to Resolve Colitis

Incidence and prevalence of inflammatory bowel disease (IBD) are increasing worldwide, especially in newly industrialized countries. Both ulcerative colitis and Crohn's disease develop from a highly complex cell-cell interaction in the intestinal mucosa, resulting in uncontrolled inflammation and tissue damage.[1] Thus, a better understanding of the inflammatory cell-cell interaction network, consisting of heterogeneous cell populations, may provide new therapeutic strategies, especially in refractory cases.

Single-cell analysis technology is rapidly emerging and used as a powerful tool to reveal the cellular heterogeneity and dynamics of various diseases.[2] The technology is also applied to analyze immune cells or epithelial cells of patients with IBD and has provided a new perspective regarding the role of those cell populations in the pathogenesis of ulcerative colitis or Crohn's disease.[3–5]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ho et al[6] report their comprehensive single-cell analysis results of a mice colitis model and features a "hub" role of stromal cells in the resolution phase of the colitis. Ho et al[6] display a comprehensive landscape of the cell-cell interaction network at various colitis phases from the time course single-cell transcriptome analysis. Through ligand-receptor analysis, they successfully identified broad and high-level cell-cell interactions linked to stromal cells. The importance of this "hub" function of stromal cells was found mainly at the resolution phase of the colitis model, mediated in part by Sepina3n, a secretory serine protease inhibitor. As expected, intravenous administration of Sepina3n showed a therapeutic effect in the colitis model, possibly through its effect on elastase activity and S100a8/9-positive neutrophils.

Compared with immune cells or epithelial cells, the importance of stromal cell function in IBD has been paid relatively low attention. However, recent studies have indicated the essential roles of stromal cells in the pathogenesis of IBD.[7] Rigorous single-cell analysis of colonic mesenchymal cells revealed a proinflammatory population of stromal cells in patients with IBD.[8] Also, functional impairment of proper development of tissue-resident mesenchymal stem cells has been reported.[9] Previous works have also shown the therapeutic effect of mesenchymal stromal cells (MSCs) in IBD disease model, mainly by its immune-modulating effect on Th1 responses or interleukin-23/interleukin-17-mediated proinflammatory signals.[10] Based on these previous findings, Ho et al's[6] present work may provide new points of view in at least 2 aspects.

First, a potential protective role of resident stromal cells has been identified in addition to its proinflammatory role in IBD. At present, it is not clear if the protective role is mediated by cells distinct from proinflammatory stromal cells. Also, the stromal cell produced protective mediators other than Serpina3n needs to be identified to precisely understand its "hub" function. Also, all the findings need evaluation and confirmation in human patient samples. However, the present study suggests stromal cells as a new cellular target of drug development. For example, enhancers of stromal cell Serpina3n production may be a good candidate for alternative IBD therapy.

Second, it may provide beneficial insight into allogeneic MSC therapy. For example, evaluating MSCs for their potential to produce Serpina3n (or its human homolog Serpin A3) may predict MSC products' effectiveness under clinical trials.[11] Further characterizing the "beneficial" stromal cell population identified by Ho et al's[6] study may provide a better way to discriminate and choose the MSC population with the highest therapeutic "hub" potential for patients with IBD.

Current therapies for IBD are developed based on the concept that regulating specific proinflammatory signals would be effective for treating patients with IBD. Targeting stromal cell "hub" function to promote resolving (or anti-inflammatory) signals may add another category of therapy that could be positioned in combination or as an alternative therapy with the existing standard therapies.

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Conflicts of interest
The authors disclose no conflicts.


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