HHS Public Access

Author manuscript

*Gastroenterology*. Author manuscript; available in PMC 2021 August 20.

Published in final edited form as:

*Gastroenterology*. 2020 April ; 158(5): 1506–1508. doi:10.1053/j.gastro.2020.02.019.

# The Cell Circuitry of Ulcerative Colitis, a New View for a Highly Complex Disease

**TAMARA PEREZ-JELDRES**,
Department of Gastroenterology, Catholic University of Chile/Hospital San Borja Arriaran, Santiago, Chile

**MANUEL ALVAREZ-LOBOS**,
Department of Gastroenterology, Catholic University of Chile, Santiago, Chile

**JESUS RIVERA NIEVES**,
Inflammatory Bowel Disease Center, Division of Gastroenterology, University of California San Diego, San Diego, California

**EDUARDO J. VILLABLANCA**
Division of Immunology and Allergy, Center of Molecular Medicine, Department of Medicine, 17176 Karolinska Institutet and University Hospital, Stockholm, Sweden

Inflammatory bowel diseases (IBD) are complex multifactorial diseases of the gastrointestinal tract, in which aberrant immune responses are believed to be triggered by environmental factors in genetically susceptible hosts. Although IBD remains incurable, cytokine targeted therapies offer amelioration of inflammation and often prolonged periods of remission. However, about 30%–50% of patients do not respond initially to therapy while others lose response over time (N Engl J Med 2005;353:2462–2476; N Engl J Med 2013;369:699–710). This is due in part to the heterogeneity of the disease, characterized by a wide spectrum of clinical phenotypes, heterogeneous course and prognosis and as already mentioned, responsiveness to therapy (Pharmacol Res 2019;3:1044). Therefore, pathophysiologic heterogeneity is thought to represent a major reason for the limited efficacy of IBD therapies, along with the fact that current drugs only target individual components of a highly complex disease process (Am J Gastroenterol 2016[Suppl];3:27–37). Concordant with this notion, our molecular unbiased stratification of patients with patients with ulcerative colitis (UC) showed that although approximately 70% of UC2 patients are responders, <10% of UC1 patients responded to anti-tumor necrosis factor (TNF) therapy (Nat Commun 2019;10:1–11). Thus, UC1 patients show significantly worse response to therapy highlighting the urgent need to further stratify patients, to tailor therapy to their individual pathophysiologic pathways.

A new precision medicine-based approach is the next challenge for IBD therapy (Inflamm Bowel Dis 2019;25:S31–S39). To achieve this objective, novel technologies that allow us to understand the molecular and cellular circuits that characterize patients subgroups are required (Inflamm Bowel Dis 2019;25:S31-S39). In this context, Smillie et al mapped the cell circuits in colonic tissues from UC patients and healthy donors using single-cell RNA sequencing. The authors analyzed cells from biopsies of 12 healthy participants and 18 patients with UC to evaluate the cellular composition in an unbiased fashion,

predict cell-cell interactions, and map IBD risk gene into cell types and pathways. They identified 51 cell subsets, including epithelial, stromal, and immune cells, and confirmed an increase in inflammatory-associated genes in noninflamed and inflamed UC compared with healthy volunteers. Cell subsets, such as mast cells, $CD8^{+}IL17^{+}$ T cells, and regulatory T cells (Treg) were increased in inflamed tissues. Distinct cellular subsets and cell-cell interaction networking in IBD was also observed in similar single cell studies in a pediatric Crohn's disease cohort. In that study, the inflamed ilea showed a cellular module they called GIMATS because it is composed of IgG plasma cells, Inflammatory Mononuclear phagocytes, Activated T cells, and Stromal cells (activated fibroblasts and endothelial cells) and was associated with resistance to anti-TNF therapy (Cell 2019;178:1493–1508).

Genes up-regulated in B cells were associated with affinity maturation and IgG class switching (Scand J Gastroenterol 2018;53:379–389), being consistent with increased infiltration of mucosal plasma cells and IgG levels in the intestinal mucosa of IBD patients (Scand J Gastroenterol 2018;53:379–389). Plasma cells may have a protective role in the colonic mucosa, since therapies that deplete plasma cells such as rituximab can induce colitis (Scand J Gastroenterol 2018;53:379–389). However, plasma cells may also produce antidrug antibodies that interfere with drug activity (Scand J Gastroenterol 2018;53:379–389). Finally, the significance of the preponderant IgG over IgA remains unclear, but may impact the microbial-mucosal interactions responsible for alterations of the microbiota observed during IBD. Additional studies to address these questions are needed.

Notably, the authors were able to delineate TNF-expressing cells during inflammation at the single cell resolution. Unexpectedly, they found that, together with activated CD4 and CD8 T cells, Treg, and follicular B cells were the highest TNF-expressing cells in inflamed tissues. Although counterintuitive, these observations suggest that depletion of subsets of Treg and/or B cell may be beneficial in UC.

Interestingly, the authors found an expansion of M-like cells, which were integrated in a network hub together with inflammation-associated fibroblasts (IAFs), inflammatory monocytes, $CD8_{+}IL17^{+}$, follicular B cells, and T reg, likely reflecting tertiary lymphoid tissues. M cells are normally found within the epithelial layer, usually over organized mucosal lymphoid tissue composed by a B-cell lymphoid follicle, reminiscent of the Peyer patch architecture (Front Immunol 2019;10:1–13). This organization allows antigens to be transferred from M cells to dendritic cells (DC) for uptake and processing, followed by presentation to T cells in the subepithelial zone. Antigens may be also detected by follicular DC and naive B lymphocytes in inducible lymphoid follicles (Front Immunol 2019;10:1–13). This organization is established by specialized stromal cells that provide cytokines and chemokines that control the localization of migrating cells to specific compartments. As an example, CCL20 attracts subepithelial DC and B cells. CXCL13 is produced by follicular DC to recruit B cells into follicles, while other stromal cells produce CCL21 to recruit DC and T cells to the interfollicular zones (Front Immunol 2019;10:1–13). Other required cytokines include RANKL, produced by stromal cells, and lymphotoxin $\alpha 1\beta 2$ that binds to lymphotoxin beta receptor (Front Immunol 2019;10:1–13). Inflammation can induce M cells de novo with cytokines overproduced during chronic inflammation and that overlap with cytokines associated with lymphoid tissue induction, such as TNF and

lymphotoxin, resulting in induction of tertiary lymphoid tissues (Front Immunol 2019;10:1–13). In this study, the role of M-type cells in UC during inflammation is supported by their high expression of CCL20 and CCL23 that attract immune cells along with their increased expression of risk genes involved in genome-wide association studies of IBD, such as NR5A2, CCL20, and JAK2.

The authors also provided potentially important insights into the mechanisms involved in primary anti-TNF resistance observed in >30% of patients with UC. Interrogating which cells express oncostatin M (*OSM*), a cytokine associated with anti-TNF response (Nat Med 2017:23;579–589), and its receptor (*OSMR*). The authors found that inflammatory monocytes and DCs expressed *OSM*, whereas IAFs expressed *OSMR*. IAFs, and inflammatory monocyte/DC2 not only were associated with OSM and OSMR gene expression, but they were also associated with drug resistance genes (IL13RA2, TNFRSF11B, and IL-11). Moreover, patients refractory to anti-TNF contained IAF in their tissues, suggesting that IAF could be a central node at the cell-cell interaction network during inflammation and represent a new cell biomarker. In addition, the relationship between TNF and OSM signaling correlated across cell subsets and drug resistance signatures, suggesting that OSM phenocopies TNF, activating downstream targets in IAFs. Finally, it is possible that blocking OSM could represent a new treatment strategy for patients in whom TNF blockade is ineffective.

The authors additionally evaluated cell–cell networking, finding distinct cellular compartments in health and decreased compartmentalization during disease, with UC-related subsets acting as a key network hub. The authors propose a rewiring of cell interactions between inflammatory fibroblasts, M-like cells, $CD8^{+}IL17^{+}$ T cells, follicular B cells, and Tregs in UC. Finally, the authors mapped 57 genome-wide association studies implicated IBD risk genes onto a cell atlas revealing that 29 of these were enriched in specific subsets and 36 were significantly differentially expressed during disease.

The authors acknowledged certain potential technical limitations during sample preparation that may result in the loss of key cell subsets, such as submucosal enteric neurons, plasmacytoid DC, and neutrophils. It is important to consider that neutrophils have an important role during inflammation as observed in our recent study, where they were associated with the lack of clinical response to anti-TNF therapies observed in UC1 patients (Nat Commun 2019;10:1–11). In addition, it would have been desirable to corroborate that the observed endoscopic remission was confirmed by histologic remission using a histologic score, such as the Geboes score. Discrepancies between histologic and endoscopic inflammation have been previously documented (Gastroenterology 2019:16;S170–171). Additionally, it would have been informative to include patients with active UC and anti-TNF-naïve patients to evaluate the cellular composition, gene expression, cell–cell interaction, and IBD risk genes pathways during active disease, without potential treatment confounders.

This study confirms that patients in endoscopic remission exhibit a distinct inflammatory signature from those with inflammation, suggesting that differences in gene expression persist, despite endoscopic remission and/or that transcription signatures precede

inflammation, similarly to what has been reported in other studies (Gut 2018;67;43–52). These findings might explain the waxing and waning natural history of untreated UC and support the need for maintenance therapy. We could envision that next-generation clinical trial end points will not include only clinical, endoscopic, and histologic remission, but also restoration of the native cellular, proteomic, and transcriptomic identity of the healthy intestine.