

## **Tissue regulation of intestinal inflammation and tolerance**

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Gut inflammation involves contributions from immune and nonimmune cells, whose interactions are shaped by the spatial organization of the healthy gut and its remodeling during inflammation. The crosstalk between stromal and immune cells is an important axis in this process, but our understanding of spatial and functional cell circuits in the gut remains incomplete. To address this challenge, we charted the cellular organization in the colon using MERFISH spatial transcriptomics. This first-of-its-kind spatial atlas of the mouse healthy, inflamed, and recovering colon revealed several inflammation-associated fibroblast states that had not been previously appreciated and demonstrated these fibroblasts have distinct gene expression profiles, spatial locations, time of emergence in disease and origins in healthy fibroblasts. We also describe the organization of unique, statistically recurrent cellular neighborhoods in the healthy colon, and their remodeling during intestinal inflammation and recovery. In parallel, we identified an innate immune pathway that imprints durable tolerance in intestinal macrophages and prevents intestinal inflammation. We found that a tissue-scale mechanism mediated by intestinal epithelial-macrophage positive feedback is required to maintain macrophage tolerance through metabolic reprogramming downstream to noncanonical IL-18 signaling. Broadly, our findings provide a framework for understanding inflammation-induced remodeling in the gut and highlight the role of intercellular crosstalk in regulating intestinal inflammation.