A single-cell RNA-seq atlas of intestinal mononuclear phagocytes

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Mononuclear Phagocytes (MNPs) have been shown to play key roles in the preservation of intestinal homeostasis. Macrophages positioned in close proximity to the gut lumen use their phagocytic and pro-inflammatory capabilities to provide protection against invading pathogens. Despite constant exposure to commensal bacteria and other luminal contents, such tolerogenic macrophages maintain a largely anergic phenotype and help to maintain homeostasis via production of the anti-inflammatory cytokine IL10 and promotion of regulatory T cell development. Most intestinal macrophage populations are known to originate from monocytes that are continuously recruited from the blood and differentiate through a multi-stage process termed the “monocyte waterfall”. Persistent loss of homeostasis in the gut – as seen in Crohn’s disease and ulcerative colitis - results in chronic inflammation that is characterised by the accumulation of MNPs that secrete pro-inflammatory mediators, promote additional leukocyte recruitment and cause tissue damage. To better understand the contributions of MNPs to intestinal homeostasis and chronic inflammation, we set out to investigate their differentiation, diversity and dysregulation in colitis. To do so, we constructed a single-cell RNA-seq atlas of Cx3Cr1+ve MNPs in the colonic lamina propria during steady state and a time-course of experimental induced inflammation using the H.hepaticus/anti-IL10R mouse model of colitis. Cells were isolated by FACS and subjected to droplet-based scRNA-Seq analysis with the 10X Genomics Chromium platform. Graph based clustering of the resulting data identified specific monocyte, macrophage and dendritic cell sub-populations that change in phenotype and abundance following loss of homeostasis. At the peak of colitis, pseudo-time analysis revealed a modified monocyte differentiation trajectory that includes a large expansion of cells expressing genes related to the regulation of acute inflammatory responses, cytokine production and toll-like receptor signalling. This work will provide new insights into the origins, diversity and roles of MNP in the healthy intestine and their disruption in conditions such as inflammatory bowel disease (IBD).

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