Exploring myeloid cell heterogenicity in the resolution of surgery induced intestinal inflammation reveals neuroprotective role for ariginase-1 macrophages.

Patients affected by intestinal inflammation suffer from episodes of intestinal dysmotility referred to as ileus. Currently, it is believed that ileus depends on a local inflammatory response mediated by myeloid cells migrating into the gut muscularis externa leading to neuromuscular dysfunction. Recent studies from our lab showed that recruitment and differentiation of monocytes are crucial for the timely resolution of inflammation. Lack of monocyte recruitment to the gut wall resulted in functional and morphological alterations of the enteric nervous system, suggestive of neuro-supportive functions of recruited monocyte-derived cells during inflammation. However, the factors and the effector molecules responsible for the pro-resolving effect is still not well understood. Using single cell RNA sequencing at the steady state, acute and the resolution phase of ileus, we observed novel heterogeneity between myeloid cell types. Trajectory analysis revealed a differentiation pattern of classical monocytes giving rise to mature macrophages (Mφs) via multiple intermediate phenotypes. During this differentiation, Ly6Clo MHCIIlo monocyte-derived Mφ subset expressed a major pro-resolving Mφ marker, arginase-1 (Arg1), and are enriched for neuro-supportive factors according to gene enrichment analysis. Regulatory network inference analysis showed multiple transcription factors differentially regulated during monocyte differentiation including PPAR-γ, a known regulator of Arg1. Our study identifies possible transcription factors at play in giving rise to Arg1 expressing neuro-supportive Mφs from recruited monocytes essential for the recovery of gastrointestinal motility after inflammation.

Keywords : macrophages, enterc nervous system, single cell RNA seq
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