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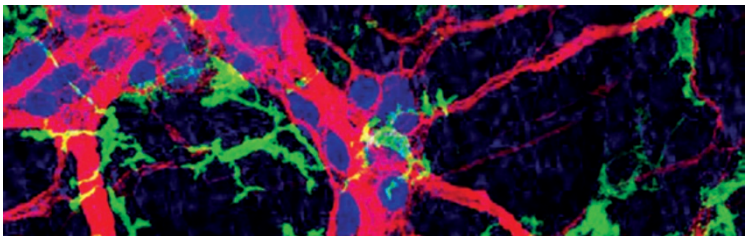
NEUROGASTROENTEROLOGY

Enteric neurons and macrophage crosstalk

Resident macrophages in the gut have unique specializations depending on their location, and neuroimmune communications between enteric neurons and macrophages shape tissue-protective responses to distal stimuli, according to new research published in *Cell*.

Tissue-resident macrophages sense and adapt to environmental cues. Within intestinal tissue, there are a wide range of macrophages, such as the mucosal or lamina propria macrophages (LpMs; close to the gut lumen) or the muscularis macrophages (MMs; located underneath the submucosa between the circular and longitudinal muscles), but limited information exists on their specific roles, especially for MMs. "MMs were identified over 30 years ago; however, little effort has been made to properly define their properties," explains author Daniel Mucida. "In particular, we wanted to know whether their different gene expression profiles, distance from the lumen of the intestine and proximity to neurons could shape their behaviour or genetic programming."

Using a variety of imaging methods and transcriptional profiling tools and experimental models, the researchers tried to understand how different environments within the gut might affect the resident macrophages. Intestingly, they observed morphological and immunological differences between MMs and LpMs in mice. By examining transcription profiles, the investigators found that LpMs expressed a proinflammatory phenotype, whereas MMs had a tissue-protective and wound-healing phenotype. Furthermore, the gene expression profile for MMs changed within a short period of time (within 2 h) in the context of infection with attenuated strains of *Salmonella*.



Confocal microscopy image of the myenteric plexus isolated from naive wild-type mouse showing enteric-associated neurons (red) and MMs (green) in close association. Courtesy of I. Gabanyi, P. A. Muller and D. Mucida.

A series of experiments revealed that MMs expressed high levels of *Adrb2* (encoding β_2 adrenergic receptors or β_2-ARs), and these MMs were in close proximity to active, firing neurons. Four layers of MMs were distinguished: serosal–longitudinal; myenteric plexus; circular muscle; and deep muscular plexus. Crucially, the researchers demonstrated a distinct neuronal circuit upon enteric infection, which led to activation of extrinsic sympathetic innervation in the gut and subsequent release of norepinephrine in the intestinal smooth muscle as well as triggering β_2-AR signalling in MMs. Importantly, β_2-AR signalling (activated via norepinephrine release) resulted in polarization of MMs and enhancement of tissue-protective programming in these immune cells.

"These observations suggest that intrinsic and extrinsic innervation are tightly integrated into the entire gastrointestinal tract response to luminal perturbations, including bacterial infections," says Mucida, adding that neurons might provide an extra layer of control over inflammatory processes in the intestine via MMs and other immune cell types. The researchers now plan further work to explore the physiological implications of these tissue-protective MMs and to understand how enteric neurons are activated by the presence of microorganisms.

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ORIGINAL ARTICLE Gabanyi, I. *et al.* Neuro-immune interactions drive tissue programming in intestinal macrophages. *Cell* http://dx.doi.org/10.1016/j.cell.2015.12.023