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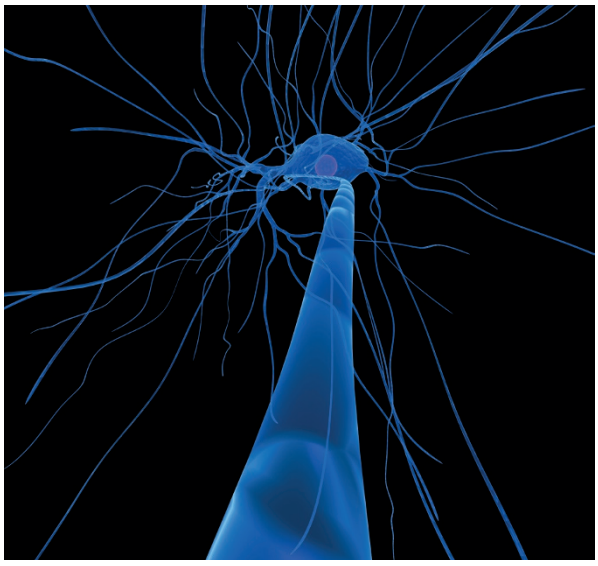
MACROPHAGES

Embracing those nerves

Tissue macrophages are highly heterogeneous populations that are shaped by the signals they encounter in their surrounding environment. Mucida and colleagues have used a range of imaging techniques to detail key differences between the macrophages found in the lamina propria of the small intestine and those that reside in the underlying muscularis layers. Notably, they describe a key role for enteric neurons and β2 adrenergic receptors in regulating the function of muscularis macrophages.

Using a deep-tissue imaging technique, the authors examined the distribution of tissue-resident macrophages in the small intestine. These experiments identified dense macrophage networks that were particularly concentrated in the lamina propria and in the muscularis of the intestine. Intravital imaging revealed that lamina propria macrophages (LPMs) and muscularis macrophages are characterized by distinct morphologies and cellular dynamics.

> “neuro–immune interactions can shape protective immunity at sites distal from an initial pathogenic assault”



Sebastian Kaulitzki/Alamy

LPMs showed slow cellular displacement in the tissue, whereas muscularis macrophages were mainly static. In addition, although muscularis macrophages formed more dendrites than LPMs, they showed reduced movement of dendritic extensions. Morphologically, muscularis macrophages could be further divided into two distinct subsets: a population of elongated bipolar cells that formed small pseudopodia, and a population of stellate cells that formed both small pseudopodia and dendritic extensions.

The authors next characterized the transcriptomes of these distinct intestinal macrophage subsets by RNA sequencing. They found that muscularis macrophages predominantly expressed tissue-protective and wound-healing genes that are typically associated with an alternatively activated (M2) macrophage phenotype. By contrast, LPMs showed a more pro-inflammatory pattern of gene expression. To examine how these gene expression profiles are affected by luminal pathogens, the authors profiled LPMs and muscularis macrophages in mice that had been orally infected with mutant strains of *Salmonella enterica* subsp. *enterica* serovar Typhimurium that do not penetrate the intestinal epithelium or that penetrate but do not proliferate. These experiments showed that the pro-inflammatory and pro-reparatory gene expression patterns seen in LPMs and muscularis macrophages, respectively, are further reinforced during luminal bacterial infection. Of note, muscularis macrophages upregulated additional M2-associated genes, including arginase 1 (*Arg1*), despite their distal location from the gut lumen.

The authors could not identify any notable differences in cytokine-, Toll-like receptor- or Fc receptor-mediated signalling in LPMs and muscularis macrophages. Therefore, they examined whether neuronal mechanisms might shape these distinct macrophage subsets. Muscularis macrophages expressed higher levels of *Adrb2* (which encodes β2 adrenergic receptor (B2AR)) compared with LPMs, and intravital imaging showed that most muscularis macrophages are located in close proximity to active neurons in the intestine. Notably, co-culture of macrophages with primary enteric-associated neurons led to the upregulation of *Arg1*, and this could be blocked by the addition of butaxamine (a specific B2AR blocker). This suggests that noradrenaline signalling through B2AR promotes an M2 phenotype in muscularis macrophages. Although myeloid cells in the gut have previously been shown to produce noradrenaline, a series of experiments indicated that most noradrenaline released into the gut muscularis is derived from extrinsic sympathetic innervation. Finally, the authors showed that treatment of mice with butaxamine impaired the upregulation of *Arg1* and other M2-associated genes in muscularis macrophages during infection with mutant *S.* Typhimurium.

In summary, extrinsic sympathetic neurons seem to reinforce a tissue-protective gene expression programme in muscularis macrophages by releasing noradrenaline during intestinal infection. Along with other recent studies, these findings show that neuro–immune interactions can shape protective immunity at sites distal from an initial pathogenic assault.

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