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Spotlight

Enteric glial cells mediate gut immunity and repair

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In the gut, coordinated cell interactions regulate tissue repair and immunity. How enteric glial cells (EGCs) mediate these processes remained elusive. In a recent paper, Progatzky *et al*. demonstrate that EGCs interact with immune and mesothelial cells under homeostasis and helminth infection, revealing an indispensable role of an interferon-γ (IFNγ)-EGC-CXCL10 axis in tissue repair.

The enteric nervous system (ENS) densely innervates the gut, but the roles of distinct ENS cell types in host defense is not well understood. EGCs are specialized astrocyte-like neuroglia that closely associate with enteric neurons and their processes, contributing to various reflexes, including those related to gut motility and secretory function [1]. EGCs can produce proinflammatory and anti-inflammatory cytokines and chemokines to modulate immune cells [1]. When it comes to tissue repair, it has been generally observed that repair processes typically rely on coordinated cellular cooperation involving both immune and non-immune cells, pointing at EGCs as potential key players in gut tissue protection. However, how precisely EGCs mediate gut protection processes has remained largely unclear.

In a recent study, Progatzky *et al*. [2] investigated the role of EGCs in tissue repair and immunity using a mouse model of *Heligmosomoides polygyrus* infection in the gut. *H. polygyrus* are helminths that, as larvae, invade the intestinal wall and can cause severe tissue inflammation [3]. Using Sox10-based strategies to label EGCs, the authors found that *H. polygyrus* infection promotes EGC proliferation and reactive gliosis in the tunica muscularis in murine small intestine. Bulk population and single-cell transcriptional analysis of EGCs showed strong upregulation of genes indicative of responses to IFNγ in *H. polygyrus*-infected mice compared with uninfected mice. To study the role of IFNγ signaling, the authors generated *Sox10-creERT2; Ifngr2$^{fl/fl}$* mice to specifically knockout this receptor in EGCs. These mice and control mice were infected with *H. polygyrus*. While the absence of IFNγ signaling had no effect on worm expulsion, the authors observed bleeding at helminth settlement sites and increased numbers and sizes of granulomas in the tunica muscularis (Figure 1). Granulomas are accumulations of immune cells surrounding a parasite [3], with persistence likely indicating impaired repair. *Ifng* transcripts as well as *Stat1* and IFNγ-response genes in both immune and non-immune cells in the tunica muscularis were lower, indicating that IFNγ signaling in EGCs is important for sustained IFNγ production. While innate immune populations increased in absence of IFNγ signaling, CD8$^+$ T cell numbers decreased 7 days postinfection, suggesting that IFNγ signaling in EGCs mediates sustained CD8$^+$ T cell expansion during early stages of helminth infection.

Further analysis identified natural killer (NK) cells and type 1 innate lymphoid cells (ILC1s) as early producers of IFNγ during *H. polygyrus* infection, with IFNγ$^+$ immune cells in proximity to EGCs. Helminth infection also induced the chemokine *Cxcl10* in EGCs in an IFNγ-dependent manner. Mice with EGC-specific deletion of CXCL10 displayed more granulomatous inflammation, indicating that EGC-mediated repair relies on CXCL10. These mice showed decreased *Ifng* expression and IFNγ$^+$ CD8$^+$ T cell numbers in tunica muscularis. The authors therefore posited that EGC-driven CXCL10 expression amplifies IFNγ production in the muscularis to mediate tissue repair. While CD8$^+$ T cells are recruited following EGC expression of CXCL10, it is still unclear how they participate in inhibiting granuloma formation.

Progatzky *et al*. [2] next addressed the question of whether EGCs interacted with other cell types in tissue repair. At homeostasis, single-cell RNA-sequencing of EGC-specific IFNγ receptor ablated mice identified changes in expression of genes associated with inflammation, mainly in three cell types: mesothelial cells, fibroblasts, and muscularis macrophages (MMs). Spontaneous inflammation in the tunica muscularis was observed in 25% of these mice. Mesothelial cells expressed fewer markers related to mesenchymal cell transition, suggesting decreased potential for tissue repair. After *H. polygyrus* infection, MMs expressed decreased levels of *Arg1*, *Retnla*, and *Chil3,* transcripts associated with tissue repair in mice lacking EGC-specific IFNγ signaling.

To add potential clinical relevance to their findings, Progatzky and colleagues [2] found a similar induction of IFNγ-response gene expression in EGCs isolated from colons of patients with ulcerative colitis compared with healthy controls, suggesting that different inflammatory stimuli may induce a related IFNγ gene signature in EGCs, even across different species (mice and humans, in this case). How this IFNγ signaling in EGCs contributes to pathology in inflammatory bowel disease remains to be determined.

The findings by Progatzky and colleagues [2] point at several interesting future directions for investigation. Recent work showed that EGC–MM crosstalk mediates visceral pain in mouse models of colitis [4]. Mechanistically, increased connexin-43 signaling in EGCs promoted production of macrophage colony-stimulating factor,

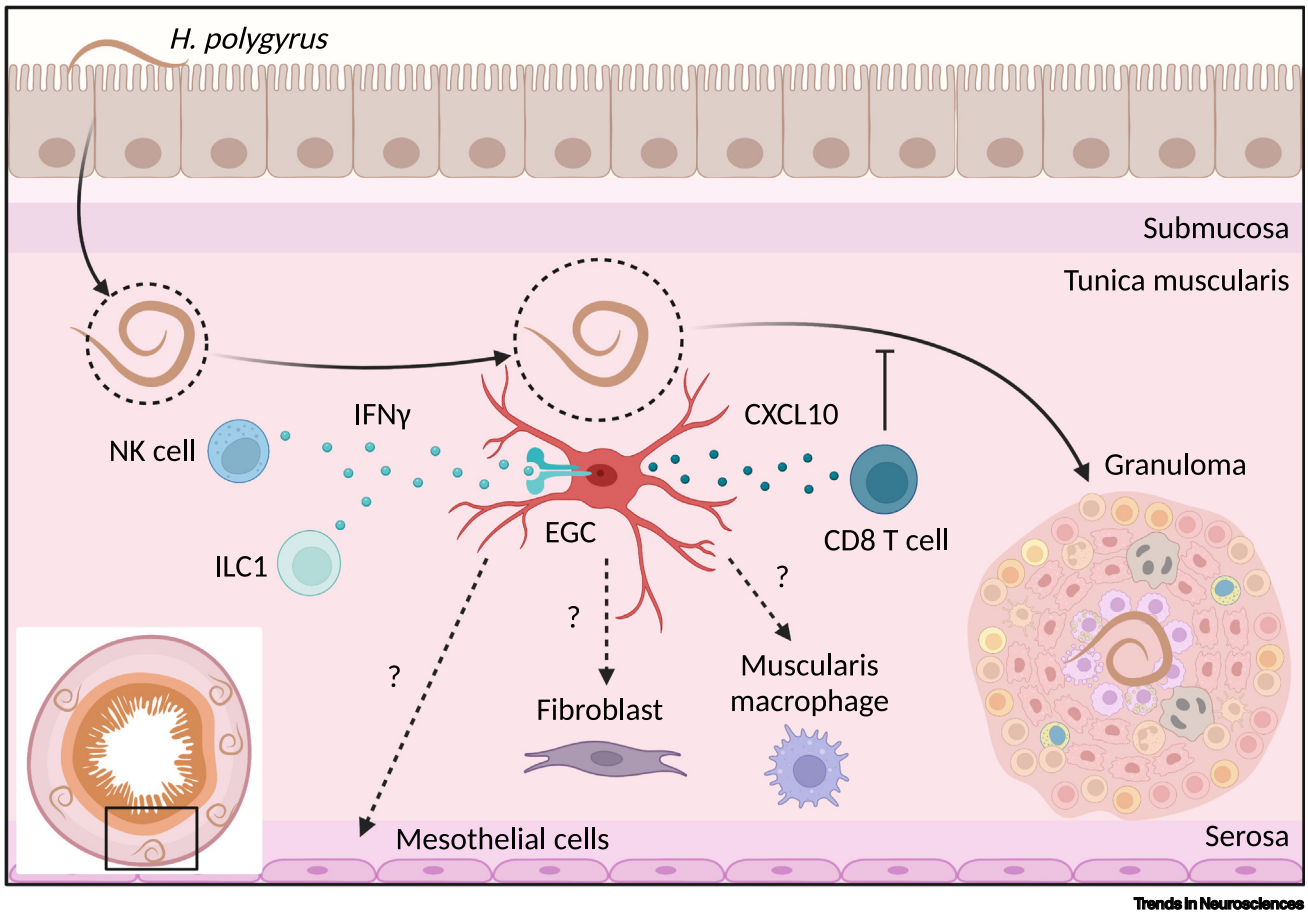

Figure 1. Enteric glial cells contribute to tissue repair after helminth infection. Progatzky *et al*. [2] show that in mice, enteric glial cells (EGCs) are activated in response to *Heligmosomoides polygyrus* infection to protect the host from granuloma formation in the tunica muscularis of the duodenum. Interferon-γ (IFNγ) produced by natural killer (NK) cells and type 1 innate lymphoid cells (ILC1s) acts on EGCs to upregulate *Cxcl10* expression. CXCL10 then recruits $CD8^+$ T cells to further amplify IFNγ and inhibit granuloma formation. Disruption of IFNγ signaling in EGCs also induces transcriptional changes in mesothelial cells, fibroblasts, and muscularis macrophages, thereby potentiating tissue homeostasis and repair. Figure created with BioRender.

which activated MMs to enhance visceral hypersensitivity [4]. This finding raises the question of whether the IFNγ-EGC-CXCL10 signaling pathway found by Progatzky *et al*. [2] also relates to pain. It is also important to understand how anatomically or molecularly distinct EGCs crosstalk with immune cell types. Recent studies showed that EGCs from both human and mice are molecularly diverse and are present throughout the gut wall, including the mucosa, suggesting a multifunctional role in regulating local cells [1,5–7]. A recent study found a role for glial fibrillary acidic protein $(GFAP)^+$ EGCs, but not proteolipid protein 1 $(PLP1)^+$ EGCs, in regulating stem cell maintenance and crypt regeneration after gut injury [8]. $GFAP^+$ EGCs provided Wnt molecules to support intestinal stem cell regeneration [8]. Other studies revealed that glial cells in the mucosa produce glial-derived neurotrophic factor (GDNF) to communicate with type 3 innate lymphoid cells (ILC3s) to enhance host defense against *Citrobacter rodentium* infection and colitis [9]. EGCs sense microbial cues and produce GDNF, which acts on ILC3s through RET signaling to promote interleukin (IL)-22 production [9]. Do the EGCs examined by Progatzky *et al*. [2] also regulate ILC biology? What are their roles in bacterial or viral infections? Furthermore, how EGCs react to other cytokines or chemokines under different contexts also remains to be elucidated.

In summary, Progatzky and colleagues [2] demonstrate that EGCs in the gut play an important role in intestinal immune homeostasis and tissue repair after infection through an IFNγ-EGC-CXCL10 axis. The study provides novel insights into EGC–immune communication in gastrointestinal inflammation. Future studies are needed to explore whether and how this axis

contributes to other inflammatory gastrointestinal disorders, including inflammatory bowel disease and various types of pathogen infection.

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Declaration of interests

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