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EDITORIAL

Glial Orchestrated Neurodegeneration: An Important Crossroad for Neural Stem Cell Therapy to the Intestine

Conventional wisdom teaches us that glia protect neurons in the human body. For more than a century, physicians and scientists have argued that glia provide the fundamental infrastructure and life support to neurons, without which the brain and intestine rapidly transcend into chaos. But what if popular consensus is wrong and our glial chaperones secretly monitor for epigenetic clues that determine whether a neuron will live or die? In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, 2 independent reports provide new mechanistic insight into how enteric neurons survive during intestinal inflammation and after neural stem cell therapy. Both studies pose interesting and immediate questions about the rationale for intestinal autologous neural transplantation, which generally assumes that host immune function is the biggest adversary to prolonged neural stem cell survival in the enteric nervous system.

Enteric neuropathy is associated with wide-ranging intestinal pathology and dysmotility: epitomized by inflammatory bowel disease and aganglionic bowel failure in Hirschsprung's disease when embryonic neural crest cells fail to colonize the distal colon. Autologous neural stem cells are actively being explored as clinical therapy for Hirschsprung's disease and hold much promise based on treatment successes already reported for hematopoietic and cardiac disease. Unlike allogenic stem cell therapy in which the recipient and donor are different people, autologous transplantation removes, expands, and later gives back stem cells to the same person to avoid immune rejection. In a mechanistic proof-of-concept study, Rollo et al[1] significantly advance our understanding of potential barriers to autologous enteric neural therapy by showing that p75+ stem cells can be isolated and cultured from postnatal Hirschsprung's colon using simulated Wnt-driven signaling. Importantly, expanded enteric neural stem cells retain the capacity to proliferate and colonize avian embryonic intestine, as well as postnatal aganglionic colon muscle cultures from the same patient. The investigators also confirm earlier reports that aneuronal colonic tissues from Hirschsprung's patients harbor a rich network of neuronal precursors and glia. These findings are encouraging because they show in vitro feasibility for postnatal autologous neural cell transfer in Hirschsprung's patients, but raise new questions. Are functional synapses formed in postnatal intestine after autologous neural stem cell transfer? Are non-neural cells in neurosphere cultures required for stem cell expansion? What is the origin of neural precursors and glia identified in aneuronal colon from Hirschsprung's patients? Sacral neural crest and glial stem cells are potential alternative neural sources, but why do these precursors not differentiate in the colon? Do neural precursors identified in these aganglionic sites also expand and colonize in vitro models? Such findings could indicate that neurons preferentially are eliminated as they differentiate, possibly by resident glial cells (Figure 1). Further studies are needed to establish exactly how receptive postnatal Hirschsprung's colon is to longer-term neural stem cell survival, especially because cellular proliferation markers such as 5-ethynyl-2′-deoxyuridine measure both DNA synthesis and alternate nucleotide salvage pathways associated with DNA repair and cell death.

Glial-driven killing of enteric neurons was shown in an elegant study by Brown et al[2] in the same issue of *Cellular and Molecular Gastroenterology and Hepatology*. Taking a lead from astrocyte biology in the central nervous system, the investigators showed that acute purine release from glial hemichannels mediate cell death signals to enteric neurons via activation of purinergic receptor P2X, ligand gated ion channel, 7 receptors. Mechanistically, a signaling cascade is initiated by extracellular adenosine diphosphate action on glial P2Y1 receptors that triggers connexin-47–dependent adenosine triphosphate release, which is rapidly toxic to enteric neurons. This purinergic feedback

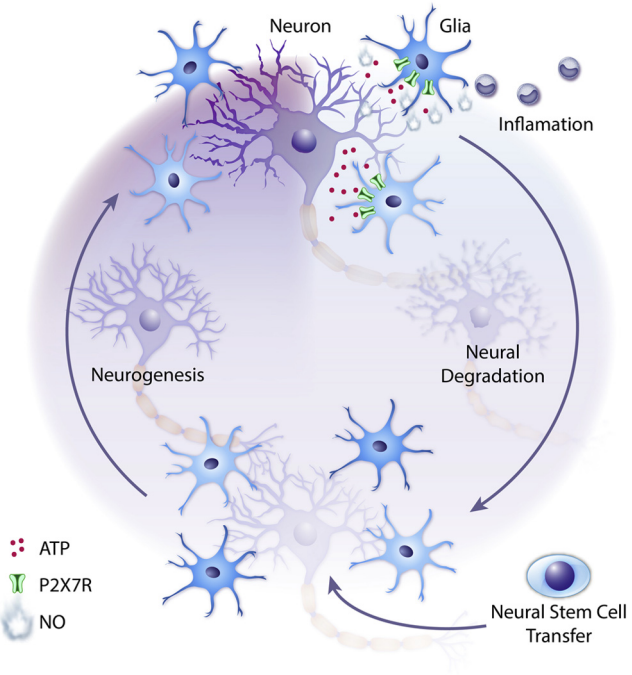

Figure 1. Neuronal-glia ineractions during intestinal inflammation and neural stem cell transfer. ATP, adenosine triphosphate; NO, nitric oxide; P2X7R, purinergic receptor P2X, ligand gated ion channel, 7.

loop appears in large part to be regulated by inflammation-generated nitric oxide, which contributes significantly toward enteric neuronal loss in vitro and in vivo. Although further work is required to establish whether nitric oxide signals also sensitize P2X7 receptors on enteric neurons and/or activate other neurotoxic mediators in glia, this intriguing observation indicates that glial cell activation may have detrimental outcomes on enteric neurons. Whether glial-induced neurodegeneration is unique to inflammation of the colon or is a general feature of glial activation in the intestine is not known. For example, glial hypertrophy and rapid neuronal loss are common findings in ischemia-reperfusion of the small intestine, whereas glial activation after vagal nerve stimulation protects the small intestine from acute trauma. Glial-derived nitric oxide also plays an important regulatory role in mucosal fluid secretion during inflammation of the colon, but not in more proximal tissues. Because enteric glia represent a highly heterogeneous cell population, it will be important to establish whether all glial subtypes relay purinergic death signals to enteric neurons. Because inflammation and infection often preferentially target the mucosa, for example, in ulcerative colitis, it will be interesting to learn whether submucosal neurons are affected similarly. It also will be important to establish whether enteric neuronal precursors are targets of these purinergic death signals.

In conclusion, enteric glial cell activation in response to central or local epigenetic signals may have evolved as pathogenic triggers of neurodegeneration in the intestine. Further studies are needed to investigate whether these previously unappreciated cell death responses represent a potential barrier to postnatal enteric neural stem cell programs.

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