Enteric Glia
The “glue” of the enteric nervous system
Keith A. Sharkey

Enteric Glia
The “Glue” of the Enteric Nervous System

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Enteric glial cells

• Anatomical and functional standpoint
• Glia play important metabolic and functional roles in terms of neurotransmission

Acknowledgements

• Dr. Brian D. Gulbransen, Department of Physiology, Michigan State University, made some of the slides in this presentation and contributed to the development of many of the ideas presented below
• Dr. Yasmin Nasser, Department of Medicine, University of Calgary, contributed to the initial development of the concepts in this presentation
• Winnie Ho and Cathy MacNaughton contributed to all aspects of the research from my lab presented below
• My thanks to the many collaborators who contributed to various studies whose data are presented below

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The gut and its brain

- The gastrointestinal (GI) tract – gut - is a vital organ for life
- The digestion of food is a complex process requiring precise coordination
- The gut has to move food along its length, digest and absorb nutrients and ultimately eliminate waste and undigested materials
  - It takes a “brain” to detect, initiate and control GI motility and regulate the processes of digestion

The gut and its brain (2)

- Digestion is itself a dangerous process; Food is rarely sterile and the processes of digestion create food antigens that themselves may be harmful
- Therefore, exposure to antigens, toxins, environmental irritants, parasites and infectious agents places an additional burden on the GI tract
  - A “brain” is required to control the processes of host defense

The gut and its brain (3)

- The “brain” in the wall of the gut is the enteric nervous system (ENS)
- The ENS is the 3rd division of the autonomic nervous system
- The ENS is composed of two ganglionated nerve plexuses:
  - The myenteric plexus lies between the external muscle layers
  - The submucosal plexus lies in the submucosa
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The anatomy of the ENS

The gut and its brain (4)

- The two ganglionated nerve plexuses consist of enteric neurons and enteric glia, and a dense neuropil that is more CNS-like than other parts of the autonomic nervous system
  - There are about as many neurons in the ENS as there are in the spinal cord
  - Enteric neurons have extensive synaptic connections and innervate the cells that make up the wall of the gut

Enteric glia

- First described by Dogiel in 1899
- Detailed anatomical characterization of ganglionic glia was made by Gabella (1970s)
Enteric glia (2)

- Cell bodies of enteric glia are smaller than enteric neurons.
- In enteric ganglia, enteric glia are irregular stellate-shaped cells.
- Enteric glia characteristically express an extensive network of gliofilaments.
- Enteric glia are derived from neural-crest progenitors.

Enteric glia (3)

- Gabella was the first to describe axonal specializations contacting enteric glia; he termed them “neuroglial junctions.”

Enteric glia surround enteric neurons

- They express glial fibrillary acidic protein (GFAP) and S100.
- Enteric glia are similar to CNS astrocytes.
- Enteric glia slightly outnumber enteric neurons.
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Enteric glia surround enteric neurons (2)

• (a) There is a similar relationship between astrocytes [green] and neurons [magenta] in the mouse cortex and (b) enteric glia [green] and enteric neurons [magenta] in the myenteric plexus.

Enteric glia surround enteric neurons (3)

• At the cellular level, enteric glia wrap around enteric neurons in a similar manner to that seen in the CNS.

Four types of enteric glia have been described in the wall of the gut.

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Four types of enteric glia have been described in the wall of the gut (2)


Mucosal enteric glia

Mucosal enteric glia regulate epithelial barrier function

Savidge et al., Gastroenterology 2007; 132: 1344-1358

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Mucosal enteric glia regulate epithelial barrier function (2)

- Co-culture of enteric glia with epithelial cells enhances intestinal barrier function – structurally and functionally

Taken from Savidge et al., Gastroenterology 2007; 132: 1344-1358

Mucosal enteric glia regulate epithelial barrier function (3)

- s-nitrosoglutathione (GSNO) has been identified as the molecule secreted by enteric glia to enhance epithelial barrier function

Taken from Savidge et al., Gastroenterology 2007; 132: 1344-1358

Mucosal enteric glia regulate epithelial barrier function (4)

- Ileal injury induced by burn injury was reduced by vagal nerve stimulation
- This effect is associated with enhanced enteric glial GFAP expression
- GSNO mimics the effects of vagal nerve stimulation on burn-injury induced epithelial permeability

Costantini et al., Am. J. Physiol. GI & Liver 2010; 299: G1308-G1318

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Enteric glia regulate epithelial cell differentiation and proliferation

- Enteric glia synthesize and secrete the PPARg ligand 15-deoxy-Δ12,14-prostaglandin J2
- This ligand inhibits epithelial cell proliferation

Taken from Bach-Ngohou et al., J. Physiol. 2010; 588: 2533-2544

Enteric glia regulate epithelial cell differentiation and proliferation (2)

- Co-culturing enteric glia with epithelial cells enhances markers of differentiation
- These effects are abrogated by blocking PPARg

Taken from Bach-Ngohou et al., J. Physiol. 2010; 588: 2533-2544

Intraganglionic enteric glia

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Enteric glia “listen” to enteric nerves

- Enteric glia in the myenteric and submucosal plexuses express receptors for many enteric neurotransmitters
- Some of these receptors elicit functional responses in enteric glia in situ
- Enteric glia potentially serve to integrate and regulate aspects of neurotransmission in the ENS

Enteric glia “listen” to enteric nerves (2)

MGluR5 activation upregulates pERK1/2 and cFos in enteric glia

Taken from Nasser et al., Glia 2007; 55: 859-872
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Use of calcium imaging to visualize activity in enteric glia

Slide from B. Gulbransen (Michigan State University)

ATP stimulates enteric glia in situ

Original data from Gulbransen & Sharkey, Gastroenterology 2009; 136: 1349-1358

ATP stimulates enteric glia in situ (2)

Original data from Gulbransen & Sharkey, Gastroenterology 2009; 136: 1349-1358

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Do enteric glia respond to neuronal activity?

Focal nerve stimulation activates glial Ca\(^{2+}\) responses _in situ_ (2)

Original data from Gulbransen et al., _J. Neurosci_. 2010; 30: 6801-6809
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Original data from Gulbransen & Sharkey
Gastroenterology 2009;136:1349-1358

Enteric glia express P2Y4 and not P2Y11

Summary
• Enteric glia respond to ATP in situ
  ➢ Likely mediated by P2Y4 receptors in GP colon MP
• Purinergic neuron-glia signaling occurs in the ENS

Original data from Gulbransen & Sharkey
Gastroenterology 2009;136:1349-1358

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Is there any selectivity to enteric glial cell activation?

Which neuronal component(s) of the ENS “talk” to glia?

Enteric glia detect activity in specific neural pathways

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Nicotinic stimulation of enteric neurons does not activate glial Ca^{2+} responses

Ave glial resp
Ave nn resp

Enteric neuron

Ave glial resp
Ave nn resp

Gulbransen et al., J. Neurosci. 2010, 30: 6801-6809

Myenteric P2X7 expression and function


P2X7-mediated enteric neuron-to-glia communication

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P2X7-mediated enteric neuron-to-glia communication (2)

Glia
Enteric neuron

Enteric neuron
Glia

Glia ectonucleotidases regulate functional responses

Enteric neuron

Pannexin-1 channels are linked to P2X receptors and can release ATP
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Neurons release ATP via pannexin-1 channels

Enteric glia detect intrinsic and extrinsic neural activity by monitoring extracellular purines

Enteric glia are activated during the colonic migrating motor complex
- Enteric glia appear to integrate neural activity during physiological motor activity in the colon

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Functional glial ablation reduces GI motor function in the mouse

- The gliotoxin fluorocitrate reduces intestinal motor function in vivo and in vitro

Gliogenesis and neurogenesis

- Inflammation of the GI tract causes glial cell division (red, BrDU; green, S100)

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GFAP expression is enhanced in colitis in GFP-GFAP transgenic mice

• Inflammation of the GI tract causes enhanced GFAP expression

Neurogenesis

• Under culture conditions and after injury enteric glia may de-differentiate and form new enteric neurons

Summary
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Enteric glia – key points

- Unique populations of glial cells reside at multiple levels through the gut wall along the length of the gastrointestinal tract
- At the level of the mucosa, enteric glia influence epithelial cells and, thus, epithelial barrier function
- Within enteric ganglia, enteric glia are similar to the astrocytes of the central nervous system, detecting and integrating neural activity
- Enteric glia have the potential to modulate enteric neurotransmission, but exactly how they influence enteric circuits is unknown
- Enteric glia have a neurogenic capacity in vitro that seems to be largely suppressed in vivo

Acknowledgements

- Funding for the original research presented above came from:

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