Defining the role of glia in the enteric nervous system

Meenakshi Rao, MD, PhD
Columbia University
October 9, 2015

Disclosures

No relevant conflicts to disclose.

Enteric nervous system (ENS)

- Can function independently of CNS
- Regulates:
  - Gastrointestinal motility
  - Secretion
  - Mucosal maintenance
  - Mucosal immunity
  - Hormonal secretion
Enteric glia are essential for GI function

- Chemical ablation (HSV-Tk + ganciclovir)
  - Severe jejunoileitis
  - Altered epithelial proliferation
  - Altered epithelial barrier
  - Neuronal degeneration

- Immune-mediated targeting of enteric glia

*These methods all targeted GFAP-expressing cells.*

Proteolipid protein 1 (PLP1) is a new marker of enteric glia

Genetic model for conditional ablation of enteric glia

**Genetic Model:**

```
Rosa26 Rosa26 LoxP LoxP
STOP DTA
PLP-CreERT: Expresses tamoxifen-inducible Cre recombinase within PLP1-expressing cells
```

**Experimental groups:**

- Cre+, Tamoxifen
- Cre-, Tamoxifen
Crypts

Villi

Ablation of PLP1+ glia does NOT result in intestinal inflammation

How does loss of enteric glia affect gastrointestinal function?

• Intestinal-epithelial barrier: No effect
• Epithelial proliferation & repair: No effect
• Enteric neurons
  • Survival: No effect
  • Function: ?
Enteric glial loss alters neuronal function

Enteric glial loss does not alter UGI transit

Analyzing colonic motility ex vivo
Summary

- Enteric glia widely express PLP1
- Conditional expression of DTA in PLP1-expressing cells is a robust, non-inflammatory model of enteric glial ablation
- Enteric glia play a sexually dimorphic role in colonic motility
  Does this underlie sex differences in functional disorders?

Thanks

Michael Gershon, M.D.
Gabriel Corfas, Ph.D.
Svetlana Sabel, M.D.
Daniella Rastelli
Lauren Dong
Sophia Chiu
Wanda Setlik
Bradlee Nelms
Michael Rutlin, Ph.D.

NASPGHAN Foundation
NIH (NIDDK)
Milton Fund
Glaxo Smith Kline
CUMC Dept. of Pediatrics
BCH Div. of Pediatric GI
Glial ablation alters colonic motility in a sex-dependent manner

Immuno-EM confirms loss of S100β+ enteric glia

Immunohistochemistry and confocal microscopy show altered expression of S100β and PLP1 in Cre+ compared to Cre- animals.
GFAP HSV-Tk mice express Tk protein in epithelial cells

Enteric glial ablation does not alter epithelial barrier penetration

Enteric glial ablation does not alter bacterial penetration
Glial ablation does not affect epithelial proliferation

![Graph showing villus to crypt ratio and Ki67+ cells per crypt for Cre- and Cre+ groups in duodenum and ileum, with no significant differences (n.s.)]