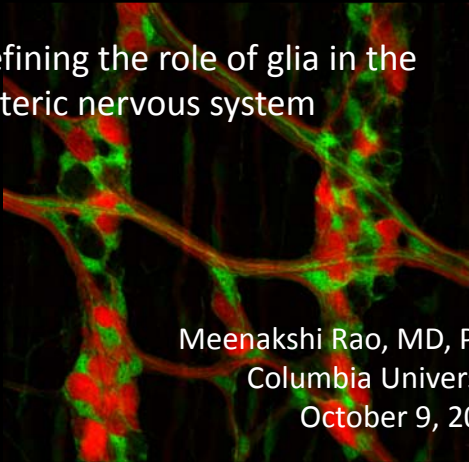


Defining the role of glia in the enteric nervous system



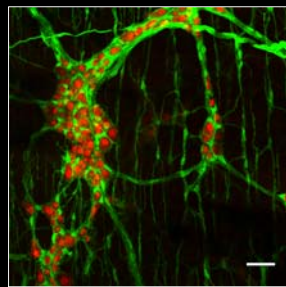
Meenakshi Rao, MD, PhD
Columbia University
October 9, 2015

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



Neurons, Glia

Enteric glia are essential for GI function

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

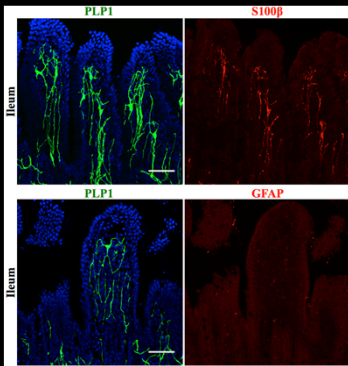


Bush et. al., Cell, 1998.

- Immune-mediated targeting of enteric glia

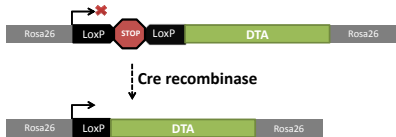
These methods all targeted GFAP-expressing cells.

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



Rao, M., et al. *Glia*, 2015.

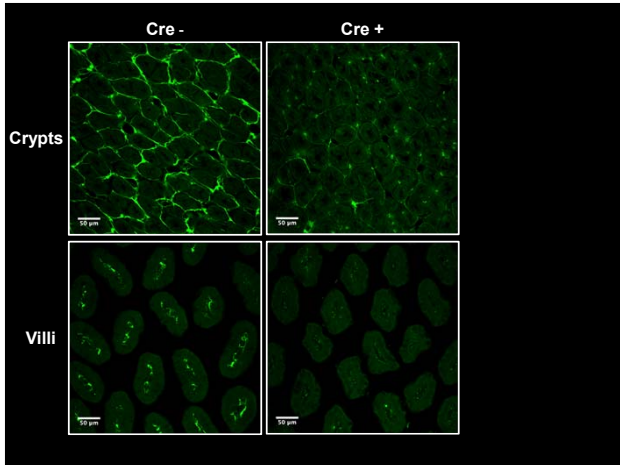
Genetic model for conditional ablation of enteric glia

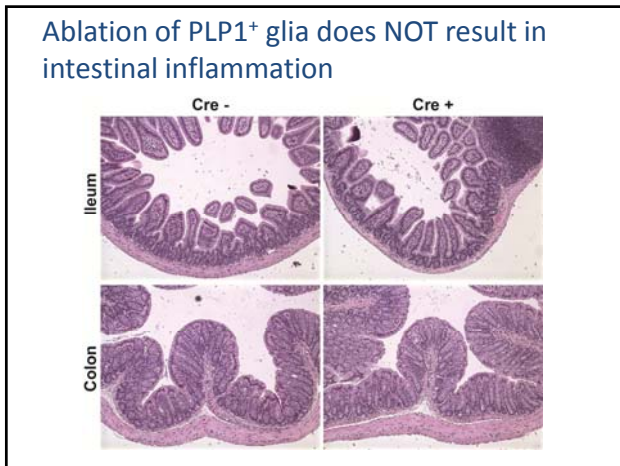


PLPCreERT: Expresses tamoxifen-inducible Cre recombinase within PLP1-expressing cells

Experimental groups:

- Cre+, Tamoxifen
- Cre-, Tamoxifen

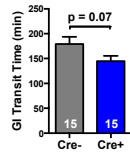




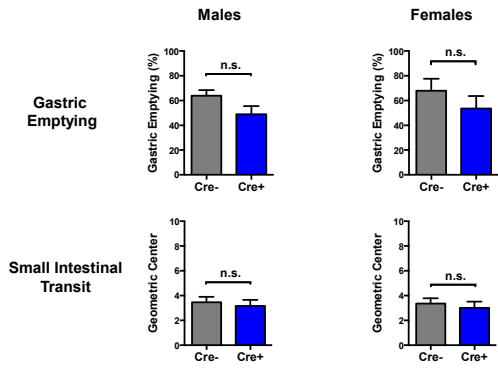
How does loss of enteric glia affect gastrointestinal function?

- Intestinal-epithelial barrier: No effect
- Epithelial proliferation & repair: No effect
- Enteric neurons
 - Survival: No effect
 - Function: ?

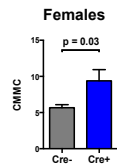
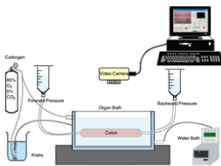
Enteric glial loss alters neuronal function



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

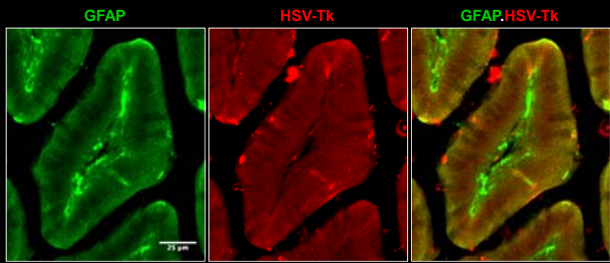
Does this underlie differences in functional disorders?

Thanks

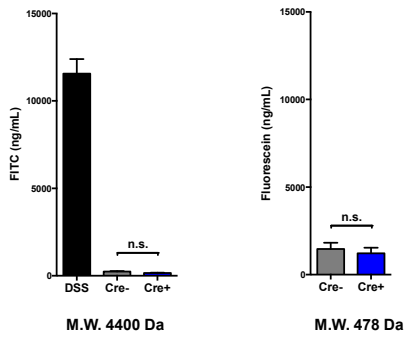
Michael Gershon, M.D.	NASPGHAN Foundation
Gabriel Corfas, Ph.D.	NIH (NIDDK)
Svetlana Sabel, M.D.	Milton Fund
Daniella Rastelli	Glaxo Smith Kline
Lauren Dong	CUMC Dept. of Pediatrics
Sophia Chiu	BCH Div. of Pediatric GI
Wanda Setlik	
Bradlee Nelms	
Michael Rutlin, Ph.D.	



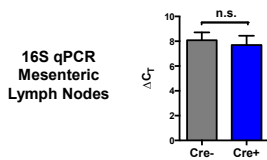
GFAP HSV-Tk mice express Tk protein in epithelial cells



Enteric glial ablation does not alter epithelial barrier penetration



Enteric glial ablation does not alter bacterial penetration



Glial ablation does not affect epithelial proliferation

