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TIPOLOGIA DI RELAZIONE Finale
TITOLO DELLA RELAZIONE: Role of C1qa muscularis macrophages in the GI motility: new potential target to control diabetic gastroparesis.

RELAZIONE:

- **BACKGROUND**

Complement 1q (C1q) complex regulates the immune responses in different organs. In the central nervous system (CNS) C1q proteins are exclusively secreted by microglia to mediate synaptic pruning during development and exert a neuro-protecting effect against pathogens and inflammation. Changes to complement-mediated mechanisms are associated with behavioral alterations in mouse models of Alzheimer's disease, aging, frontotemporal dementia, and virus infection (Cho, 2019). Recently, a population of macrophages, called muscularis macrophages (MMs) showing a similar phenotype to microglia, has been identified in the muscularis propria of the gut. The gut muscularis propria houses enteric neurons and plays a central role in the coordination of GI motility. Diabetic Gastroparesis (DG) is a neuromuscular disorder that occurs mainly in patients with type 1 and type 2 diabetes and is associated with abnormal gastric motility, visceral hypersensitivity, and mucosal inflammation (Egboh and Abere, 2022). The pathophysiology of DG is still unclear, however, changes to MMs phenotype are considered central to its development (Chikkamenahalli et al. 2021). In addition, the complement pathway is negatively correlated with DG symptoms, in humans and mice (Grover et al., 2019).

Thanks to single cell data analyses of FACS sorted immune cells (CD45+ cells) from the muscularis layers of GI tract of both humans and mice, we recently observed a cluster of MMs characterized by the expression of C1qa (unpublished data). Although the role of the C1q family in the CNS is well defined, in the gastrointestinal tract it is still completely unknown, thus we first studied the role and function of C1qa in homeostatic conditions, determining its distribution in the MMs population. After that, we evaluated the impact of C1qa MMs in GI physiology, to verify its potential role as pharmacological target for the treatment of DG.

- **EXPERIMENTAL APPROACH**

By using a KO mouse (CSF1rC1qa) model in which was conditionally removed C1qa from macrophages, I study the effect of this population on GI motility.

- **RESULTS**

- The analysis of the physical parameters reveals no differences between CSF1rC1qa and WT mice regarding body weight and length; however, CSF1rC1qa mice are characterized by a longer GI tract compared to WT mice, mainly due to a longer small intestine.
- CSF1rC1qa mice have a faster whole-gut transit time (about 1 hour) than age-matched controls mice. Breaking down these results, I found no differences between experimental groups in solid gastric emptying, while I observed an accelerated small bowel transit time.
- The C1qa protein expression is higher in the colon, followed by the stomach and the small intestine. Whole-mount immunohistochemistry and 3D-reconstruction analysis showed that C1qa MMs are mainly located within the myenteric plexus of all the small intestine and the colon, a gut layer housing the enteric neuronal bodies. Using a

triple staining whole-mount immunohistochemistry I found that C1qa MMs are mainly associated with the enteric neurons.

- Since in the CNS, microglia secreted C1qa affect neurons, I checked the possible contribution of C1qa secreted by MMs on enteric neurons. The small intestine and the colon of CSF1rC1qa mice showed a higher expression of the primary synaptic markers (PSD95 and SYP) compared to WT mice, both at protein and gene levels.

➢ CONCLUSIONS

Here I identified a novel population of MMs expressing C1qa, in the GI tract. This new population of C1qa MMs affects GI motility by regulating synapse formation and proper communication between enteric neurons, suggesting its potential use as a new pharmacological target for the control of DG.

➢ REFERENCES

1. Cho K. Emerging Roles of Complement Protein C1q in Neurodegeneration. Aging Dis. 2019;10, 652-663. doi:10.14336/AD.2019.0118.
2. Egboh C and Abere S. Gastroparesis: A Multidisciplinary Approach to Management. Cureus vol. 2022; 14,e21295.doi:10.7759/cureus.21295.
3. Chikkamenahalli LL, Pasricha PJ, Farrugia G, Grover M. Gastric Biopsies in Gastroparesis: Insights into Gastric Neuromuscular Disorders to Aid Treatment. Gastroenterol Clin North Am. 2020; 49, 557-570. doi: 10.1016/j.gtc.2020.04.009.
4. Grover M, Dasari S, Bernard CE, Chikkamenahalli LL, Yates KP, Pasricha PJ, Sarosiek I, McCallum R, Koch KL, Abell TL, Kuo B, Shulman RJ, Gibbons SJ, McKenzie TJ, Kellogg TA, Kendrick ML, Tonascia J, Hamilton FA, Parkman HP, Farrugia G. Proteomics in gastroparesis: unique and overlapping protein signatures in diabetic and idiopathic gastroparesis. Am J Physiol Gastrointest Liver Physiol. 2019; 317, 716-726. doi: 10.1152/ajpgi.00115.2019.

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