UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

Tutor's Name	Prof.ssa Maria Cecilia Giron
Cotutor's Name	

1) Project title: ***EXPLORING THE ROLE OF ENTERIC NERVOUS SYSTEM ON MYELINATION DURING EARLY LIFE***

2)Abstract (max 500 words)

The enteric nervous system (ENS) is an extensive neuronal network, embedded in the gastrointestinal (GI) tract, that holds sensing machinery for monitoring luminal microbiota-derived perturbations. Since GI microbial colonization and central nervous system (CNS) development occur during a critical window in neonatal life, exposure to dysbiotic events, such as stress or infection in infancy, can disrupt the development of microbiota-gut-brain (MGB) axis, leading to neuropsychiatric disorders (NPDs; e.g., major depressive disorder (MDD), autism spectrum disorders (ASD)). Most neural axons are unmyelinated at birth. During infancy oligodendrocytes ensure rapid myelination, that slowly consolidates spatiotemporally until adulthood to ensure neurotransmission. The prefrontal cortex, undergoing later myelination in newborn, is affected by neonatal intestinal dysbiosis, and highly implicated in NPDs. Intriguingly, the ENS expresses myelin and contains glial cells that share transcriptome features of oligodendrocytes, supporting the hypothesis that ENS is involved in the neuroinflammatory process that disseminates to the CNS. Whether and how NPDs are linked to the gut is of increasing importance given emerging reports that NPDs are transmitted from the gut to the brain. We found that antibiotic-induced dysbiosis or TLR2/TLR4 deficiency in mice leads to significant morpho-functional ENS changes and altered myelinization, characterized by modified gut motility and susceptibility to neuroinflammation which can be rescued by intraperitoneal administration of GDNF or TLR2 agonists. Following on these findings, we posit that gut dysbiosis causes myelinization changes similar to those seen in NPDs, resulting in ENS neuroinflammation, altered GI motility and impaired cognition, and depends on host-microbiota interactions. The proposed multidisciplinary study will integrate the science of neurogastroenterology with neuropsychopharmacology. This hypothesis will be tested with three aims performed in the cuprizone mouse model. First, we will evaluate whether cuprizone administration causes disrupted myelinization, neuroimmune changes and neuronal loss. Second, we will assess whether disruption in gut motility precedes impaired cognition. Finally, using experimental manipulation of the microbiota, we will explore the role of host-microbiota interactions in NPDs-associated GI disease and their relationship to cognition. Specifically, we will examine whether and how NPDs progression is affected by antibiotic-mediated dysbiosis, or TLR2 stimulation. Successful completion of the proposed studies will identify critical pathophysiological pathways that affect the gut and precede the onset of NPDs. The results will inform novel prevention and intervention strategies for NPDs and cognitive dysfunction during infancy.