UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title: **INTESTINAL NEUROIMMUNE RESPONSES IN NEURODEGENERATIVE DISORDERS: THE ROLE OF MICROBIOTA-GUT-BRAIN AXIS**

2)Abstract (max 500 words)

Multiple Sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the central nervous system (CNS) among young adults. MS etiology is still unknown and involves genetic predisposition together with environmental, immunoregulatory and microbiome-derived factors. The enteric nervous system (ENS) contains glial cells that share transcriptome features of CNS oligodendrocytes and astrocytes, including myelin proteins. Alterations in ENS function could be responsible for the bowel symptoms commonly observed in MS patients. Indeed, recent studies have revealed ENS nerve fiber loss, gliosis and neuronal damage, occurring prior to the development of CNS lesions in MS patients and related animal models. ENS plays a key role in immunity regulation and the immune Toll-like receptor 4 (TLR4) is known to influence MS pathogenesis. 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 modulation of TLR2/4 signaling. Moreover, alterations in gut microbiota composition appears to contribute to intestinal and blood-brain barrier disruption, immune cells infiltration into the CNS and neurodegeneration. Gut microbiota deficiency, obtained by antibiotic treatment or using germ-free mice, significantly reduces MS-related neurodegeneration whereas microbiota restoration with probiotics or TLRs modulation decreases the demyelination process suggesting that probiotics treatment might be a promising approach for MS treatment. Following on these findings, we posit that gut dysbiosis causes myelinization changes similar to those seen in MS, 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 recognized preclinical MS models. First, we will characterize the role of TLR4 signaling during MS development, by depicting TLR-dependent immune-mediated pathways leading to intestinal neurodegeneration and spreading of the pathology to CNS. Second, we will assess the impact of gut microbiota-immunity interaction on demyelinating process by pharmacologically depleting Gram+ bacteria population. Finally, using experimental manipulation of the microbiota with probiotics or specific TLRs ligands, we will explore the role of host-microbiota interactions in MS-associated GI disease and their relationship to cognition and disease severity. Successful completion of the proposed studies will identify critical pathophysiological pathways that affect the gut and precede the onset of MS. The results will inform novel prevention and intervention strategies for MS. During the 3-year PhD training the candidate will acquire knowledge in assessing ENS dysfunction and the role of microbiota-gut-brain axis in neurodegenerative diseases as well as methodological skills in i) transfer of knowledge and communication, both in written and

oral forms, ii) overcoming challenges in experimental design and analysis execution, iii) enhancing expertise to design new preclinical and clinical research.