UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

EXPLORING THE NEUROIMMUNE CROSSTALK IN INFLAMMATORY BOWEL DISEASES

2) Abstract (max 500 words)

Inflammatory bowel diseases (IBD), (e.g. Crohn's disease and ulcerative colitis), are chronic, recurring, inflammatory conditions of the gut. Although IBD exact aetiology is unknown, it is considered a multifactorial disease with gut mucosal immune system, microbiota, genetic and environmental factors all playing a role in the pathogenesis. The enteric nervous system (ENS) is increasingly recognized as a key regulator of immune responses. Indeed, ENS through the production/release of several neurotransmitters, including dopamine and serotonin, can modulate the immune system and be a major contributor to IBD pathogenesis. The ENS dysfunction, described in IBD patients, appears to be not only a consequence of inflammatory-driven neuroplasticity but an active player in disrupting gut homeostasis. Indeed, individuals with IBD has increased incidence of psychiatric disorders, cognitive impairment and Parkinson's disease. However, the impact of peripheral inflammatory processes on brain function and behavior in IBD remains incompletely understood. The majority of IBD-associated specific mutations include genes involved in microbial recognition, such as mutations in the Toll-like receptor 4 (TLR4). TLR4, beside controlling host-defense responses, modulates ENS gut motility and repair processes following an insult and tissue repair as well as brain plasticity and remodeling. The microbiota influences TLR4 expression and tryptophan (TRP) metabolism, which, in turn, affects microbiota composition as well as host immunity promoting TLR4 sensitivity. We have recently discovered that TLR4 deficiency in mice leads to significant structural and functional ENS alterations, characterized by gut dysmotility and reactive gliosis, together with dysregulated hippocampal circuitry. This project will investigate whether an altered gut neuroimmune dialogue mediated by TLR4 and serotoninergic pathways is responsible of ENS dysfunction, ultimately leading to higher IBD severity and brain remodeling. This goal will be pursued by two well-established teams with solid experience in pharmacology and gastroenterology, based at the University of Padova (Italy), in collaboration with other European scientists from academia and pharmaceutical companies. Both groups have shown in preclinical and clinical settings the influence of microbiota in pathological conditions and the association of gut dysbiosis or anomalies in TLR signaling to ENS disruption and hypersensitivity to inflammation. Thus, we will investigate whether a TLR4-mediated ENS dysfunction is responsible in affecting IBD pathogenesis through tryptophan-derived metabolites. This research project aims to i) decode the impact of defective TLR4 signaling on ENS and CNS integrity, gut microbial composition and tryptophan-derived metabolites; ii) evaluate the influence of TLR4 on the microbiota-gut-brain axis in experimental colitis; iii) decipher the protective role of dietary tryptophan in the microbiota-gut-brain axis during experimental colitis. This project will take advantage of cutting-edge neuromolecular methods and functional assays to reveal the microbiome-gut-brain signature in experimental IBD and decode the endogenous biochemical signals contributing to intestinal inflammation, potentially leading to the development of more effective therapeutic interventions in IBD.