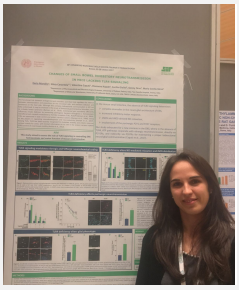
ImmunoTools *special* Award 2018



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Exploring the neuroimmune crosstalk in functional inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of recurring debilitating inflammatory conditions. IBD etiology is still vague and involves the complex interaction of genetic, environmental, immunoregulatory and microbiome-derived factors *[1]*. In the gut, resident bacteria confer many benefits to intestinal physiology and have a truly mutualistic relationship with the host *[2].* However, inappropriate activation of the immune system by pathogens and also commensal bacteria appears to play crucial importance in the pathogenesis of intestinal disease *[3].* 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.

However, a still open question on ENS role in IBD is whether a neuropathy may per se affect gut homeostasis, by influencing the immune machinery and generating a favorable environment for the onset of deregulated inflammatory responses. The majority of IBD-associated specific mutations includes genes involved in microbial recognition, such as mutations in the Toll-like receptor 4 (TLR4). Beside controlling host-defence responses, TLR4 modulates ENS activity, gut motility and repair processes following an insult. Innate immune response relies on toll-like receptors (TLRs), able to recognize conserved molecular motifs found in microbes or damaged cells *[4].* In the gut, my group and others have shown that: i) TLRs are expressed not only on immune and epithelial cells but also on neurons, glia and myocytes *[5];* ii) TLR4 knockout mice show altered gut motility and inhibitory neuromuscular responses *[4];* iii) TLR2 and TLR4 blockade markedly affects serotoninergic pathways *[6]*; iv) impaired TLR2 signalling disrupts structural and functional ENS integrity with consequent higher susceptibility to inflammatory damage *[5].* Intriguingly, changes in serotonin and dopamine levels, deregulated serotoninergic/dopaminergic machinery and altered TLRs expression have been consistently associated with IBD in patients and in animal models *[7-8-9]*. The regulation of the immune system via ENS

modulation appears an attractive field of research and hold promise for treating IBD by possibly taking advantage of the many neuroactive drugs in clinical use.

Therefore, we intend to investigate whether a TLR4-mediated ENS dysfunction is responsible in affecting IBD pathogenesis through dopaminergic/serotoninergic pathways. This research project, therefore, aims to i) decode the functional role of TLR4 signalling in gut neuroimmune crosstalk in animal models of colitis; ii) evaluate the enteric neuroimmune crosstalk in IBD patients by a pilot clinical study. This project will embrace a multidisciplinary approach including biochemical and neuromolecular studies in mouse models of colitis and IBD patients to unravel the gut neuroimmune signature of IBD. The ELISA kits selected from the ImmunoTools panel will facilitate further profiling of gut neuroimmune crosstalk in intestinal biopsies and plasma samples of colitis animal models and IBD patients. These data will be combined with alterations in gut neuroimmune signature obtained from animal studies in order to design a predictive algorithm of IBD severity and potential therapeutic effectiveness.

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4) *Caputi V, et al. Front Pharmacol. 2017 Jun 8; 8:350.*
5) *Brun P, et al. Mol Cell Neurosci. 2015; 68:24-35*
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