PERSPECTIVE

# Cross-talk between T-cells and gut-microbiota in neurodegenerative disorders

**The emerging role of gut microbiota as a key player in the development of neurodegenerative disorders:** Mammals have evolved together with commensal microbiota to establish a symbiotic relationship in which they regulate reciprocally by synthesizing and responding to several common chemical substances. In this regard, gut microbiota constitutes a consortium of bacteria that not only participates in the degradation of nutrients, but also produces metabolites, fatty acids and neurotransmitters that can act on the enzymes and receptors expressed in eukaryotic cells, which considerably affects the physiology of the host and contribute to maintaining homeostasis (Lyte, 2013).

According to the important role that gut-microbiota plays in maintaining homeostasis, alterations in the composition of gut-microbiota (dysbiosis) have consistently been involved in the development of neuropsychiatric, metabolic, autoimmune and neurodegenerative disorders. With respect to this last point, human and animal model researches have shown that the presence of some precise bacteria or the absence of some beneficial components in the gut microbiota of genetically susceptible individuals could trigger the development of Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS). For instance, an increase of *Proteus mirabilis* in the composition of gut microbiota and excess production of short-chain fatty acids in the intestinal mucosa have been shown to promote the development of PD in several animal models (Sampson et al., 2016; Choi et al., 2018). On the other hand, it has been demonstrated that the butyrate producing bacteria, *Butyrivibrio Fibrisolvens*, was selectively decreased in the intestinal microbiota of animals genetically susceptible to ALS, and the administration of butyrate significantly attenuated the disease development disease (Zhang et al., 2017). Notably, in a study conducted with 34 pairs of discordant twins for MS, the results show that the composition of the intestinal microbiota from healthy twins was different from that obtained from twins with MS (Berer et al., 2017). Furthermore, using a mouse model of MS that develop the disease spontaneously in a specific-pathogen-free environment, the experiment showed that the mice developed a severer disease when they received the transfer of gut-microbiota from twins with MS than from healthy twins (Berer et al., 2017). Significant dysbiosis has also been implicated in AD patients, including the alteration in the composition of several bacterial taxa, such as *Bacteroides Actinobacteria*, *Ruminococcus*, *Lachnospiraceae* and *Selenomonadales* (Zhuang et al., 2018). Supporting these data obtained from AD patients, studies conducted in mouse models and recently also in *Drosophila* have shown that dysbiosis of the intestinal microbiota produces cognitive deterioration and neurodegeneration. Thus, the composition of gut microbiota plays a fundamental role in controlling homeostasis in central nervous system (CNS), and avoiding neurodegenerative disorders.

**T-cells play a fundamental role in the pathophysiology of neurodegenerative disorders:** So far, four non-excluding mechanisms have been proposed to explain how gut commensals could regulate host homeostasis: i) By secreting or affecting the production of mediators (*i.e.*, neurotransmitters, neuropeptides or metabolites) that could directly stimulate their receptors in the neurons of the enteric nervous system, thereby generating neural signals that directly affect the intestinal physiology or migrate through the vagus nerve to the CNS, affecting behaviour or neuroinflammation (Lyte, 2013). ii) By the production of metabolites and hormones in the intestinal tract that can diffuse through the intestinal wall, entering the blood circulation, and then affect the function of distant organs, such as adrenal glands and liver (Lyte, 2013). iii) By affecting the expression of tight-junctions in intestinal epithelial cells and, therefore, regulating gut permeability to bacterial components, thus preventing or promoting inflammation. iv) By generating mediators that affect the enzymes or stimulate the receptors expressed in the immune cells present in the gut mucosa, thus shaping the lymphocyte phenotype, which can later infiltrate the brain affecting behaviour and/or neuronal survival (Arpaia et al., 2013; Campos-Acuna et al., 2019).

It is noteworthy that among the immune cells affected by the metabolites produced by the intestinal microbiota, $CD4^+$ T-cells have been shown to be highly relevant in the development of chronic inflammation and neurodegenerative disorders. Thereafter, a large number of studies carried out in animal models have consistently shown that neurodegenerative disorders involve an autoimmune component mediated by autoreactive $CD4^+$ T-cells with inflammatory phenotypes, including Th1 and Th17 cells (Gonzalez et al., 2015). Interestingly, $CD4^+$ T-cell deficient animals are resistant to the development of PD, AD and MS, whilst animals devoid of T-cells develop an exacerbated disease manifestation in ALS models (Gonzalez et al., 2015). Furthermore, recent studies have shown the involvement of autoreactive $CD4^+$ T-cells specific to β-synuclein or to β-synuclein in PD and MS patients, respectively (Sulzer et al., 2017; Lodygin et al., 2019). Thereby, increasing evidence indicates that an autoimmune response mediated by Th1 and Th17 lymphocytes plays a critical role in the pathophysiology of neurodegenerative disorders. At this point, is important to note that regulatory $CD4^+$ T-cells (Treg), which have the ability to inhibit the inflammatory reaction exerted by Th1 and Th17 cells, become key roles of attenuating neuroinflammation and neurodegeneration.

**$CD4^+$ T-cells as mediators between dysbiosis and the development of neurodegeneration:** Emerging evidence has indicated that short-chain fatty acids, including acetate, propionate, butyrate and pentanoate, can shape responses mediated by $CD4^+$ T-cells, affecting the differentiation and expansion of inflammatory and anti-inflammatory phenotypes. Similarly, glutamate, dopamine, γ-aminobutyric acid, serotonin and other mediators whose concentrations in the intestinal mucosa depend on the composition of the microbiota, constitute also a group of molecular cues controlling the inflammatory behaviour of T-cells (Gonzalez et al., 2015; Campos-Acuna et al., 2019). For instance, the stimulation of the G-protein coupled receptor 41 by propionate or butyrate attenuates T-helper-2 (Th2)-mediated allergy, whilst the G-protein coupled receptor 43 stimulation exerted by acetate or propionate strongly favours the immunosuppressive activity and the expansion of Treg cells (Arpaia et al., 2013). Similarly, it has been shown that stimulation of low-affinity dopamine receptors promotes anti-inflammatory features in T-cells, whereas signaling triggered by the stimulation of high-affinity dopamine receptors in these cells has consistently been involved in the induction of pro-inflammatory phenotypes, including Th1 and Th17 (Gonzalez et al., 2015). In addition, glutamate favours have been shown to Th1-mediated responses, whilst γ-aminobutyric acid has been shown to be an anti-inflammatory signal for $CD4^+$ T-cells, attenuating Th1 responses and favouring Treg activity (Gonzalez et al., 2015).

Importantly, it has been suggested that autoreactive $CD4^+$ T-cells could be activated in the gut either by encountering their cognate antigens in the gut-associated lymphoid tissues in an inflammatory context or by molecular mimicry. For instance, $CD4^+$ T-cells specific for the interphotoreceptor retinoid binding protein are activated in the gut and differentiate in the inflammatory Th17 phenotype in a microbiota-dependent manner, even in interphotoreceptor retinoid binding protein-deficient mice (Horai et al., 2015). Furthermore, studies has shown the generation of pathogenic forms of α-synuclein in the gut mucosa, which is associated with intestinal inflammation in early stages of PD, even before motor deterioration in patients and animal models (Campos-Acuna et al., 2019). Therefore, considering all these findings together, it is tempting to hypothesize that autoreactive T-cells involved in neurodegenerative disorders would be activated in gut-associated lymphoid tissues and a pathologic composition of intestinal microbiota would promote the acquisition of inflammatory phenotypes in these cells, such as Th1 and Th17. Subsequently, autoreactive Th1 and Th17 lymphocytes would promote neuroinflammation and neurodegeneration associated with the corresponding pathology (**Figure 1**). To validate or refute this hypothesis, future efforts should focus on acquiring causal evidence demonstrating the interdependence between the composition of the gut microbiota, the activation of autoreactive $CD4^+$ T-cells and neurodegeneration in animal models of AD, PD, MS and ALS. Moreover, the association of dysbiosis with the expansion of autoreactive populations of $CD4^+$ T-cells in patients suffering from these neurodegenerative disorders would also be key evidence. These kinds of studies would help to answer key pending questions in this area, including: i) Are autoreactive T-cells involved in neurodegeneration activated in the gut? ii) Is the pro-inflammatory phenotype of autoreactive T-cells involved in neurodegeneration induced by the altered intestinal microbiota? iii) Is the activation of these autoreactive T-cells

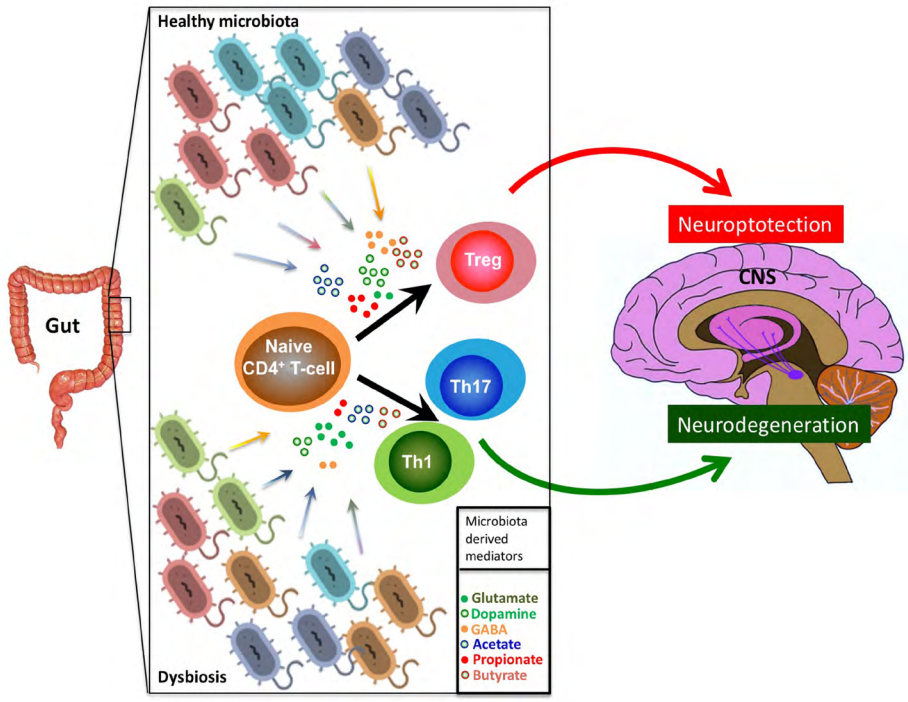


**Figure 1 CD4$^+$ T-cell response as a major mediator in the cross-talk between gut microbiota and neurodegeneration.**
In homeostasis, the mixture of molecular cues produced by healthy microbiota promotes the differentiation of naïve autoreactive CD4$^+$ T-cells in Treg cells, thus promoting tolerance to self-constituents and neuroprotection. Conversely, upon dysbiosis, the consequent alteration in the composition of molecular cues that affect CD4$^+$ T-cells would displace the differentiation of autoreactive naïve CD4$^+$ T-cells towards the inflammatory phenotypes Th1 and Th17. Subsequently, autoreactive Th1 and Th17 cells would infiltrate the brain and promote neuroinflammation and neurodegeneration. Pro-inflammatory lymphocytes promoting neurodegeneration are indicated in blue and green. Immunosuppressive lymphocytes promoting neuroprotection are indicated in red. Different colours of bacteria and molecular signals are used to represent diversity. CNS: Central nervous system; GABA: γ-aminobutyric acid.

induced by some components of the gut microbiota with molecular mimicry with CNS antigens? iv) Are the CNS-derived antigens delivered into the gut-associated lymphoid tissues to be presented to T-cells? In addition, these studies would help to decipher the code of "beneficial" and "detrimental" bacteria, considering as early therapeutic targets in genetically susceptible individuals. The future validation of the cross-talk of gut microbiota with autoreactive T-cells in the development of neurodegenerative disorders can also potentially show early biomarkers of these pathologies, including the presence of "detrimental" bacteria or the absence of "beneficial" bacteria in the gut microbiota, the presence of pathogenic protein inclusions (*i.e.*, α-synuclein fibrils) in the intestinal mucosa, or the presence of T-cells reactive to CNS self-constituents in peripheral blood.

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