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 secreted 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 (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. In this respect, human and animal studies 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 by butyrate producing bacteria, Butyrylribio Fibrisolvens, was selectively decreased in the intestinal microbiota of animals genetically susceptible to ALS, and the administration of butyrate, 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., 2019).

Cross-talk between T-cells and neurodegeneration in animal models: Emerging evidence has indicated that short-chain fatty acids, including acetate, propionate, butyrate and pentanoate, can modulate responses mediated by CD4+ T-cells, changing their homing properties 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). 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, it 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 modulate responses mediated by CD4+ T-cells, changing their homing properties 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 down-regulation of inflammation in Th17 (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 the immunosuppressive 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 have 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). It is possible to correlate the consequences of dysbiosis with the acquisition of 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 alteration of dysbiosis in 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
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 mucusa, or the presence of T-cells reactive to CNS self-constituents in peripheral blood.

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