

Evidence of Host–Microbiome Interactions triggering “Gut-first” Parkinson’s disease

M. Munoz Pinto^{I,III}, E. Candeias^{I,III}, A.R. Esteves^{I,III}, D. Nunes-Costa^{I,III}, I. Melo-Marques^I, J.D. Magalhães^{I,III}, D.R. Carneiro^{I,IV}, M. Sant’Anna^V, A.R. Pereira-Santos^{I,III}, S. Alarico^{I,II}, I. Tiago^{VI}, A. Morgadinho^{IV}, P.N. Figueiredo^V, C. Januário^{IV}, N. Empadinhas^{I,II}, **S. Morais Cardoso^{I,VII}**

^ICenter for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal, ^{II}IIIUC - Institute for Interdisciplinary Research, University of Coimbra, Portugal, Coimbra, Portugal, ^{III}Ph.D. Programme in Experimental Biology and Biomedicine (PDBEB), Institute for Interdisciplinary Research (IIIUC), University of Coimbra, Coimbra, Portugal, ^{IV}Department of Neurology, CHUC - Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, ^VDepartment of Gastroenterology, CHUC - Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, ^{VI}Centre for Functional Ecology, University of Coimbra, Coimbra, Portugal, ^{VII}Institute of Cellular and Molecular Biology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Parkinson’s disease (PD) is a multifactorial neurodegenerative disease characterized by the loss of dopaminergic neurons in the midbrain. In the prodromal phase several autonomic symptoms including constipation are correlated with increased α -synuclein pathology in peripheral tissues. Herein, we hypothesized that PD patients gut microbiota-mediated intestinal immune alterations triggers PD-related neurodegeneration. For this purpose, we challenged the gut-immune-brain axis of wild-type mice (WT) through colonization with human fecal material from a healthy-control (HC) and a PD patient.

We observed a clear reduction of tyrosine hydroxylase-positive (TH+) cells in the midbrain and motor dysfunction in PD transplanted mice. In addition, we observed the loss of segmented filamentous bacteria (SFB) in the ileum-associated mucosa, with subsequent increase in gut inflammation, intestinal barrier disruption and CD4+ infiltration. Intestinal leak allowed an increase in pro-inflammatory cytokines in the blood, compatible with systemic inflammation, and a blood brain barrier (BBB) permeabilization in PD mice. Interestingly, we also observed that a caudo-rostral mitochondrial dysfunction correlated with an accumulation of α -synuclein aggregates, which may be involved in the activation of neuronal innate immunity and neuroinflammation. Altogether, our results suggest that a PD dysbiotic gut may trigger PD in WT mice.