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

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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.