

ROLE OF MICROBIOTA DERIVED SHORT CHAIN FATTY ACIDS IN α -SYNUCLEIN AGGREGATION AND SEEDING

Giulio Pasinetti, Risham Singh and Lap Ho

Icahn School of Medicine, Mount Sinai, USA

Objective: To determine whether microbiome derived short chain fatty acid (SCFA) may modulate abnormal α -synuclein misfolding and seeding activity of α -synuclein to support the hypothesis of potential novel therapeutic approaches.

Background: There is growing evidence from both *in vivo* and *in vitro* studies that in many neurodegenerative disorders, including synucleinopathies, cell-to-cell transmission of a pathological, misfolded protein occurs and may be a vehicle for spreading of pathology throughout the brain. We hereby investigate whether microbiota-derived SCFAs may help attenuate the misfolding of α -synuclein and their effects on seeding synucleinopathy.

Design/Methods: *In vitro* aggregation of α -synuclein in the absence or in the presence of SCFAs at a molar ratio of 1:1 or 1:4 α -synuclein:SCFA, were monitored by using independent assays: photo-induced cross-linking of unmodified proteins assay, thioflavin-T, fluorescence assay, or electron microscopy.

Results: We found that select microbiome-derived SCFAs significantly interfere with α -synuclein aggregation in independent *in vitro* assays.

Conclusions: Selected microbiome-derived SCFAs may help protect against diverse synucleinopathies by converting dietary fibers into biologically available SCFAs which significantly interfere with aggregation of disease-specific α -synuclein into toxic aggregates. Ongoing cell-based systems, which detect levels of α -synuclein by fluorescent FRET signalling, will clarify the impact of this anti-aggregation activity of SCFAs on interference of α -synuclein seeding activity that is critical for the propagation of α -synuclein mediated pathologies. This data will help to clarify distinct α -synuclein seeding activity from α -synuclein isolated from post-mortem brain samples of patients with Parkinson's disease, multiple systemic atrophies, and other synucleinopathies, leading to novel therapeutic approaches

Giulio.pasinetti@mssm.edu