

Does Microglial Activation Influence Propagation of Alpha-synuclein Pathology

<https://neurodegenerationresearch.eu/survey/does-microglial-activation-influence-propagation-of-alpha-synuclein-pathology/>

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Country

USA

Title of project or programme

Does Microglial Activation Influence Propagation of Alpha-synuclein Pathology

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

457568.8073

Start date of award

15/02/2016

Total duration of award in years

2

Keywords

alpha synuclein, Microglia, Pathology, Lipopolysaccharides, Interleukin-4

Research Abstract

? DESCRIPTION (provided by applicant): Neuron-to-neuron propagation of ?-synuclein (?-syn) aggregates is thought to contribute to the pathogenesis of Parkinson's disease (PD) and underlie the stereotypical progression pattern of ?-syn neuropathology. This postulate suggests that aggregated ?-syn transfers from one neuron to another where it seeds further ?-syn aggregation. However, it is not known how microglia influence this process, and how specific microglia activation states that occur upon inflammation affect ?-syn transfer. To fill this gap i

knowledge we developed a unique mouse model that allows us to monitor α -syn prion-like propagation between neurons. Our in vivo paradigm involves transplantation of embryonic midbrain neurons into the striatum of a mouse overexpressing human α -syn and allows the manipulation of microglia (i.e. ablation or specific activation). In this novel model, the presence of human α -syn within the grafted mouse cells (initially devoid of human α -syn) is used as a read-out for α -syn transfer. Based on our preliminary data we hypothesize that under normal conditions, microglia take up α -syn from the extracellular space, resulting in reduced α -syn transfer from neuron to neuron. We also hypothesize that α -syn accumulates in microglia following lipopolysaccharide treatment, as lipopolysaccharide -activated microglia have reduced proteolytic capacity whereas Interleukin 4-induced microglia effectively reduce the pool of extracellular α -syn, and thereby mitigate α -syn transfer from neuron to neuron. Two specific aims will be pursued to test this hypothesis: 1) Determine how the absence of microglia affects neuron-to-neuron transfer of α -syn; and 2) Determine how the presence of lipopolysaccharide-induced vs Interleukin 4-induced activated microglia affects the rate of neuron-to-neuron transfer of α -syn. First, we will monitor if the absence of microglia results in a different degree of α -syn cell-to-cell transfer using our unique in vivo model of cell-to-cell transfer. Second, we will assess the transfer of α -syn into grafted neurons in the context of distinct microglial phenotypes. Lipopolysaccharide or Interleukin 4 injection will be used to stimulate these differential phenotypes. Our approach is innovative because it allows us to assess the interaction between two factors (inflammation and α -syn propagation) both considered to play key roles in PD pathogenesis in a single animal model, and we can define outcomes using unbiased, automated and quantitative measures of neuropathology. We predict that the absence of microglia will translate to increased neuron-to-neuron transfer of α -syn and that the nature of microglial activation will affect the accumulation of α -syn within microglia. Ultimately, the proposed research will result in an innovative and valid model of α -syn pathology propagation with the potential to facilitate the development of disease-modifying therapies based on treatments that modulate inflammation.

Further information available at:

Types:

Investments < €500k

Member States:

United States of America

Diseases:

N/A

Years:

2016

Database Categories:

N/A

Database Tags:

N/A