Does Microglial Activation Influence Propagation of Alpha-synuclein Pathology

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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 ?-syn prion-like propagation between neurons. Our in vivo paradigm involves transplantation of embryonic midbrain neurons into the striatum of a mouse overexpressing human ?- syn and allows the manipulation of microglia (i.e. ablation or specific activation). In this novel model, the presence of human ?-syn within the grafted mouse cells (initially devoid of human ?-syn) is used as a read-out for ?-syn transfer. Based on our preliminary data we hypothesize that under normal conditions, microglia take up ?-syn from the extracellular space, resulting in reduced ?-syn transfer from neuron to neuron. We also hypothesize that ?-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 ?-syn, and thereby mitigate ?-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 ?-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 ?-syn. First, we will monitor if the absence of microglia results in a different degre of ?-syn cell-to-cell transfer using our unique in vivo model of cell-to-cell transfer. Second, we wil assess the transfer of ?-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 ?-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 ?-syn and that the nature of microglial activation will affect the accumulation of ?-syn within microglia. Ultimately, the proposed research will result in an innovative and valid model of ?-syn pathology propagation with the potential to facilitate the development of disease-modifying therapies based on treatments that modulate inflammation.

Further information available at:

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