Exosomes and Neuroinflammation in Parkinsons Disease

https://neurodegenerationresearch.eu/survey/exosomes-and-neuroinflammation-in-parkinsons-disease/

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Country

USA

Title of project or programme

Exosomes and Neuroinflammation in Parkinsons Disease

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NIH (NINDS)

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01/02/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

exosome, alpha synuclein, neuroinflammation, Parkinson Disease, Microglia

Research Abstract

? DESCRIPTION (provided by applicant): Neuroinflammation has been implicated as a major pathophysiological process of Parkinson’s disease (PD) in recent years. Among various neuroinflammatory triggers, protein aggregates have been shown to be a predominant

pathological trigger for microglial activation and subsequent proinflammatory cytokine and chemokine production in the brain, which in turn con tributes to the accelerated progression of neurodegenerative processes. Also, emerging evidence indicates that aggregated pathogenic proteins, including ?-synuclein (?Syn), are packaged into exosomes, which propagate protein aggregates from affected neurons to other brain cells, including microglial cells, through a non-cellular autonomous process, leading to a heightened neuroinflammatory response. Despite these advances, the cellular mechanisms underlying microglia-mediated neuroinflammatory events following stimulation with ?Syn aggregates and ?Syn-containing exosomes are yet to be defined. While studying kinase signaling in PD models, we unexpectedly discovered that the major non-receptor tyrosine kinase Fyn is rapidly activated in primary microglia within a few minutes of stimulation with the known inflammogen LPS. Interestingly, Fyn activation triggers proinflammatory responses, including cytokine/chemokine release from microglia. In addition, our preliminary findings revealed that aggregated ?Syn also induced a rapid activation of Fyn kinase and the NLRP3 inflammasome. To further expand our novel preliminary results, we will systematically pursue the following specific aims: (i) to characterize the mechanism of Fyn kinase activation and its role in the regulation of NLRRP2/3 inflammasomes in microglia and astrocytes during inflammatory stress induced by ?Syn aggregates and exosomes containing ?Syn aggregates and to determine the proinflammatory role of Fyn in dopaminergic neuronal cell death, (ii) to define the molecular mechanisms underlying Fyn upregulation in microglia and astroglia during sustained inflammatory responses induced by ?Syn aggregates and ?Syn exosomes in animal models of PD, and (iii) to determine the role of Fyn in mediating the proinflammatory response in the nigrostriatal dopaminergic system during ?Syn protein aggregation in animal models of PD as well as in postmortem PD brain tissues. Biochemical, cellular and neurochemical approaches will be used to achieve these specific aims. Taken together, delineating the role of Fyn kinase in ?Syn protein aggregation-induced microglial activation will not only provide novel mechanistic insights into the progression of neurodegenerative processes in PD, but may also be useful for translating mechanistic outcomes into effective therapies for PD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Neuroinflammation plays a major role in the pathophysiology of Parkinson’s disease, characterized by persistent activation of microglia resulting in excessive release of proinflammatory cytokines and chemokines. Since protein aggregates have been shown to trigger a neuroinflammatory response in PD, our proposed study will characterize the role of Fyn kinase activation during a-synuclein aggregates induced neuroinflammation using cell culture and animal models. The outcome of the study will provide new insights into neuroinflammatory mechanisms of Parkinson’s disease as well as facilitate development of novel therapeutic strategies for Parkinson’s disease.

Further information available at:

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Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

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