Complement-Microglia Interaction in Synaptic Loss and Neurodegeneration in HD

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USA

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Complement-Microglia Interaction in Synaptic Loss and Neurodegeneration in HD

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3

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, Microglia, Huntington gene, Nerve Degeneration, Complement 1q

Research Abstract

DESCRIPTION (provided by applicant): (HD) is the most common autosomal dominant neurodegenerative disorder (NDD), and is characterized by involuntary movement, cognitive

and psychiatric symptoms, and relentless disease progression. HD is caused by a CAG repeat expansion in the mutant Huntingtin (mHTT) gene; however the molecular mechanisms underlying HD pathogenesis remain poorly understood. Currently, there is an urgent need to validate novel therapeutic targets to prevent or modify HD pathogenesis. Growing evidence suggests that a hallmark of age-dependent NDDs, including HD, is early neuronal dysfunction and loss of CNS synapses, followed by progressive neurodegeneration. Recent research supports an unexpected role of the complement system in synaptic pruning during development and disease. During development, and in a mouse model of glaucoma, complement proteins C1q and C3 localize to synapses and mediate synapse elimination. Our recent studies support a model in which “”weaker”” or less active synapses in the developing brain are “”tagged”” by complement and then eliminated by microglia, the primary phagocytic immune cells in CNS that express phagocytic complement receptors (i.e. CR3/Cd11b). We propose that similar complement and microglia-dependent mechanisms contribute to synapse loss, which in turn is crucial to pathogenesis of behavioral deficits and selective neurodegeneration in HD. Complement upregulation and microglial activation have been observed in human HD brain tissue and several HD mouse models, and our substantial new data showed complement factors (C1q and C3) are upregulated and tagged the synapses in the vulnerable brain regions (i.e. striatum) with known synapse loss in a full-length mHTT HD mouse model (BACHD). Recent study from Yang lab showed that behavioral deficits, selective brain atrophy and striatal synaptic toxicities in BACHD mice dependent on interaction between cortico-striatal neuronal interactions. Based on these strong preliminary data, we hypothesize that the complement system contributes to early stages of HD pathogenesis through complement- and microglia-mediated synaptic loss as a result of reduced cortico-striatal neuronal activity in HD mice. To test this hypothesis, we will study an innovative conditional HD mouse model developed by the Yang lab to determine whether complement targets cortico-striatal circuits for elimination, and whether optogenetic restoration of neuronal activities or genetic reduction/therapeutic antibody-based inhibition of the complement cascade (C3 and C1q) could ameliorate synapse loss, neurodegeneration, and behavioral impairments in HD mice. Our study could validate complement cascade (e.g. C3) and its interactions with microglia as a critical mechanism in HD pathogenesis, and provide support on the inhibition of this pathway in HD therapy.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is one of the most common inherited fatal neurodegenerative disorders characterized by progressive motor, cognitive, and psychiatric symptoms. Our proposed study is based on new findings on the influence of complement factors and their interaction with resident innate immune cells in the brain in pathogenesis of HD-like progressive movement disorder and neurodegeneration. Elucidating the precise underlying mechanisms and validating the disease impact of complement factors in independent HD mouse models may provide a novel therapeutic strategy for HD and related age-dependent neurodegenerative disorders.

Further information available at:

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Investments > €500k

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United States of America

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Huntington's disease

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