Investigating CD47-SIRPa as novel protective signals during CNS synaptic pruning

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Country

USA

Title of project or programme

Investigating CD47-SIRPa as novel protective signals during CNS synaptic pruning

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NIH (NINDS)

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15/03/2015

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4

The project/programme is most relevant to:

Huntington's disease

Keywords

CD47 gene, Microglia, Synapses, Huntington Disease, Eating

Research Abstract

? DESCRIPTION (provided by applicant): Microglia, the brain’s resident immune cells and phagocytes, are emerging as critical regulators of developing synaptic circuits in the healthy

brain. Recent studies from our lab and others indicate that microglia engulf synapses in the developing brain; however, how microglia know which synapses to target remains a major open question. Our previous work demonstrates that microglia-mediated pruning underlies developmental synaptic refinement, an essential process required for the formation of mature circuits in which weak or inappropriate synapses are eliminated and remaining connections are maintained and strengthened. We found that microglial engulfment of presynaptic inputs is activity-dependent and driven by complement molecules C1q and C3, and microglial complement receptor CR3. These molecules are innate immune “”eat me”” signals known for promoting macrophage phagocytosis of apoptotic cells or debris, and mice lacking these signals exhibit reduced microglial engulfment of synaptic inputs and impaired refinement. This suggests that microglia-mediated pruning may be analogous to the removal of non-self material by phagocytes in the immune system. However, we do not yet know how microglia precisely determine which inputs to engulf and which to avoid, an important decision regarding the specificity needed to sculpt precise, mature connections. We propose that protective “”don’t eat me”” signals are required to prevent inappropriate microglial engulfment of necessary connections during synaptic refinement, just as they prevent inappropriate engulfment of healthy self-cells by phagocytes during an immune response. Our preliminary data support this hypothesis, as “”don’t eat me”” signals CD47 and SIRP? are present in the developing brain and required to prevent excess microglial engulfment of synaptic inputs. We will investigate the anatomical, functional, and behavioral abnormalities in mice lacking CD47 and SIRP? to better understand the consequences of excess microglial engulfment. We will also investigate whether and how these “”don’t eat me”” signals are regulated by activity to determine if they direct microglia to engulf specific synapses in an activity-dependent manner. Finally, as “”don’t eat me”” signals are known to be downregulated in the brains of patients with neurodegenerative diseases, we will examine whether these molecules are dysregulated in mouse models of Huntington’s disease (HD) and could thereby underlie synapse loss caused by aberrant microglial engulfment. This study would be the first to demonstrate that synaptic protection is required to prevent inappropriate microglial engulfment of necessary connections during development. This research program will provide insight not only into the mechanisms regulating microglial engulfment of specific synapses, but also into possible mechanisms underlying synapse loss in CNS neurodegenerative diseases.

Lay Summary
PUBLIC HEALTH RELEVANCE: Microglia, the immune cells and phagocytes in the brain, organize brain circuits by engulfing inappropriate synapses. In this study, we will identify the molecular cues by which microglia recognize the target synapses, their regulation by synaptic activity, and possible involvement in neurodegenerative diseases with an emphasis on Huntington’s disease. This project will provide novel insights into the mechanisms regulating appropriate brain circuit establishment by microglia and may lead to novel treatment of neurodegenerative diseases such as Huntington’s disease.

Further information available at:

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Investments > €500k

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United States of America

Diseases:

Huntington's disease

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