TAM receptor control of microglial function and nervous system homeostasis

https://www.neurodegenerationresearch.eu/survey/tam-receptor-control-of-microglial-function-and-nervous-system-homeostasis/

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Country

USA

Title of project or programme

TAM receptor control of microglial function and nervous system homeostasis

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NIH (NINDS)

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15/09/2013

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2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Nervous System Physiology, Phagocytosis, Microglia, Neuraxis, Homeostasis

Research Abstract

DESCRIPTION (provided by applicant): Deficiencies in the control of central nervous system (CNS) inflammation precipitate or exacerbate a plethora of debilitating human diseases, yet our

understanding of the basic mechanisms that regulate neuroinflammation is incomplete. Microglia, the distinctive tissue macrophages of the brain and spinal cord, are key players in this process. These sentinel cells display two activities that are fundamental to the maintenance of neural homeostasis – (i) immune surveillance and (ii) the phagocytosis of apoptotic cells (ACs) and membranes. Studies of macrophages outside of the CNS have demonstrated that both of these activities are strictly controlled by signaling through TAM receptor tyrosine kinases. Although TAM receptors are also prominently expressed by microglia, the importance of TAM signaling to microglial activation and function in the CNS is – remarkably – unknown. The experiments of this proposal address this question. In Aim 1, genetic and cell biological methods that rely on TAM receptor and ligand mouse mutants will be used to assess the importance of TAM signaling in the homeostatic, non- inflammatory phagocytosis of ACs that occurs continuously in the healthy mammalian brain. In Aim 2, similar methods, coupled with confocal and two-photon imaging of microglia in vivo, will be used to determine the role of TAM signaling in the localized phagocytosis that underlies synaptic pruning and the remodeling of neuronal connections in postnatal neural development. In Aim 3, a series of pro- and anti- inflammatory challenges will be applied to TAM receptor- and ligand-deficient mice to determine if inhibition of the innate inflammatory response in microglia is under TAM control, as it is in cells of the immune system. Finally, in Aim 4, the knowledge gained from the earlier aims will be applied to investigate the role that TAM regulation plays in neurodegeneration, as assessed in both acute and progressive mouse models of Parkinson’s disease. Together, these studies will delineate the basic molecular, cellular, and physiological features of a fundamentally new pathway of immune homeostasis in the CNS, and potentially identify TAM receptors and ligands as new targets for therapeutic intervention in neuroinflammatory and neurodegenerative disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Defective control of inflammation in the central nervous system often results in a devastating impairment of neural function, and is thought to contribute to Alzheimer’s disease, Parkinson’s disease, Multiple Sclerosis, and many other forms of human neurodegeneration. An understanding of the basic cellular and molecular mechanisms that regulate and constrain neuroinflammation, as will be advanced by the studies of this proposal, is therefore of paramount importance to the improvement of public health.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Parkinson's disease & PD-related disorders

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