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Targeting the peripheral immune system to modify neurodegeneration

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The peripheral immune system has long been hypothesized to modulate neurodegeneration. However, the molecular mechanisms that underlie the modulation of neurodegeneration by the immune system have not been fully elucidated. Recent studies in our laboratory have found that genetic or pharmacological manipulation of the peripheral immune system is sufficient to modulate neurodegeneration in mouse models of Huntington's disease (HD) and Alzheimer's disease (AD). In a transgenic mouse model of HD, inhibition of the enzyme kynurenine 3-monooxygenase (KMO) in blood cells by a novel small molecule we generated called JM6 extended life span, prevented synaptic loss, and decreased microglial activation. JM6 also prevented memory deficits, anxiety-related behavior, and synaptic loss in a transgenic mouse model of AD. In a second study, genetic deletion of cannibinoid receptor type-2 (CB2) in peripheral immune cells dramatically accelerated the onset of motor and neuropathological deficits in two independent HD mouse models. Conversely, a peripherally restricted CB2 agonist was neuroprotective. These findings support a critical link between blood cells and neurodegeneration that is mediated by KMO and CB2 receptors. Modulation of these proteins may represent novel therapeutic approaches to treat neurodegenerative diseases.

Biography

Paul Muchowski obtained his Ph.D in Biological Structure at the University of Washington in Seattle, and did post-doctoral studies with Ulrich Hartl at the Max Planck Institute for Biochemistry and Stanley Fields at the University of Washington. He is a Senior Investigator at the Gladstone Institutes and a Professor in Biochemistry and Biophysics, and in Neurology, at the University of California, San Francisco. He is also Co-Director of the Taube-Koret Center for Huntington's Disease Research. His research focuses on elucidating molecular mechanisms of neurodegenerative diseases associated with protein misfolding, with a specific goal to identify disease-modifying pathways.

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