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Targeting astrocytes as a therapeutic strategy for Alzheimer's disease

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Abstract

Recent advances in cell-type specific research tools have led to a growing appreciation for the role of neuroglia in CNS disorders. Astrocytes are a major glial-subtype that perform vital metabolic functions and interact extensively with synapses and microvessels, which show high vulnerability in Alzheimer's disease (AD). At early stages of AD, "activated" astrocytes exhibit pronounced morphologic and biochemical changes, offering a largely-untapped source of druggable targets. Previously, we demonstrated that calcineurin (CN)/NFAT signaling is elevated in astrocytes early in AD and recapitulates many components of the activated phenotype. Our ongoing work exploits the activation status of the astrocytic CN/NFAT pathway in an attempt to (1) dissect the functional impact of activated astrocytes and (2) assess the therapeutic potential of these cells in experimental models of AD. Recently, we used adeno-associated virus (AAV) vectors bearing the astrocyte-specific Gfa2 promoter to deliver a CN/NFAT inhibitor (i.e. VIVIT) selectively to hippocampal astrocytes of APP/PS1 mice at the outset of amyloid pathology (Furman et al., 2012 J Neurosci). At 10-months-post-injection, these mice exhibited less glial activation, reduced amyloid deposition, and improved synaptic and cognitive function relative to mice treated with control AAV vectors. Ongoing studies are investigating the mechanistic basis for the neuroprotective actions of AAV-Gfa2-VIVIT and are determining if similar beneficial effects occur when treatment is administered at late disease stages. The results provide some of the first direct evidence that activated astrocytes help drive neurologic dysfunction during AD and provide proof-of-principle for the development of similar astrocyte-based strategies for treating AD.

Biography

Christopher M. Norris received his Ph.D. in Neuroscience from the University of Virginia in 1998. After finishing his postdoctoral work at the University of Kentucky in 2004, Dr. Norris joined the Sanders-Brown Center on Aging where he is now an Associate Professor. His work focuses on astrocyte signaling in aging, injury, and disease with particular emphasis on the protein phosphatase calcineurin. Dr. Norris received a NIA Career Development Award in 2004 to investigate the relationship between calcineurin and multiple aging biomarkers and is the PI of an NIA R01 grant on calcineurin and neuro inflammatory signaling, presently in its seventh year.

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