Regulation of hippocampal plasticity and learning and memory by a bloodborne rejuvenation factor

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Research Abstract

Aging is the major risk factor for Alzheimer’s disease (AD), leading to cellular and functional changes within the brain that culminate in dementia and cognitive decline. Lessening or reversing brain aging may delay Alzheimer’s disease onset or even protect against Alzheimer’s pathogenesis, having a large effect on quality of life and health burden imposed by AD. This proposal tests the hypothesis that young plasma reverses hippocampal decline in plasticity and learning/memory in the aged brain through regulation of transcriptional programs, including gene networks involving Alzheimer’s pathogenesis. TIMP2 is a key blood-borne factor enriched in young plasma that enhances hippocampal Activator-protein 1 (AP-1) and other plasticity markers, while reversing hippocampal cognitive decline in aged mice. Experiments will examine young plasma-mediated and TIMP2-mediated enhancement of AP-1, a transcriptional regulator of genes involved in hippocampal function, including MMPs that are intimately tied to amyloid-? metabolism. I will investigate the role of TIMP2 in mediating transcriptional changes in plasticity and Alzheimer’s-related genes in the aged hippocampus and the extent to which TIMP2 is a necessary factor for the beneficial effects conferred by young plasma. The mechanism by which TIMP2 improves hippocampal function, including its site of action, duration of its transcriptional control, and the effect of long-term increased TIMP2 activity on limiting cognitive decline in aged mice will be investigated. The results may inform therapies directed at restoring TIMP2 function as a treatment for Alzheimer’s disease. To fully characterize transcriptional changes induced by both young plasma and blood-borne TIMP2, Aim 1 will use next-generation sequencing methods (RNA-seq and ChIP-seq) in aged hippocampal tissue from mice treated systemically with young plasma, TIMP2, or control. ChIP-seq will be performed to identify all genes bound and regulated by AP-1 following treatment. Aim 2 assesses the necessity of TIMP2 for the cognitive improvements and transcriptional changes (identified in Aim 1) mediated by young plasma. Mice treated with young plasma will be compared to those receiving TIMP2-depleted (or KO) plasma or control. Aim 3 examines TIMP2’s site of action for improvements in aged hippocampal function (peripheral vs central) using a neutralization approach. The duration of TIMP2’s transcriptional regulation following treatment and the transcriptional and cognitive consequences of long-term peripheral TIMP2 expression using a viral-mediated approach will be pursued. Together, these aims critically assess the role of systemic TIMP2 in reversing hippocampal cognitive decline as a means to limit the impact of Alzheimer’s disease.

Further information available at:

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