Mediator as a transducer of amyloid precursor protein-dependent nuclear signaling

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a profoundly debilitating neurodegenerative disorder without effective treatment or determinative antemortem diagnostics. Improvements in diagnostic and treatment options will require a better understanding of the biological processes that drive AD onset and progression. The prevailing

model to explain AD pathogenesis holds that neuronal degeneration and clinical demise are precipitated by the gradual accumulation, in brain centers controlling memory and cognition, of amyloid-? (A?) peptide, a catabolite of the transmembrane Amyloid Precursor Protein (APP). However, recent studies suggest a complex etiology for AD, particularly for its idiopathic late-onset variety, that may involve the contribution of amyloid-independent mechanisms. Amyloidogenic processing of APP into A? concurrently liberates a small APP intracellular domain (AICD) that enters the nucleus and induces the expression of genes implicated in AD pathology. Although amyloid-independent, this APP-dependent signaling pathway is nonetheless tightly linked to A? production, suggesting that pathologic accumulation of A?, as occurs in AD, could be paralleled by an increase in concentration-dependent AICD-mediated target gene induction. Accordingly, AICD-target genes could represent both early biological indicators of A?-induced pathology as well as functional effectors of amyloid- independent pathogenic triggers. Enhanced mechanistic insight into AICD-mediated transcription control could identify new therapeutic targets and candidate markers for AD. In this regard, we recently discovered that the AICD activates transcription by targeting MED12, an RNA polymerase II transcriptional Mediator subunit implicated in human cognitive development. To identify downstream effectors of Mediator-dependent APP nuclear signaling, we profiled the transcriptomes of mouse neural progenitors following depletion of APP or MED12. Our data reveal a significant contribution of Mediator to AICD-dependent transcription control genome-wide, and further implicate the AICD and Mediator in the coordinate upregulation of neural genes in the hippocampus of AD patients compared to controls. We therefore hypothesize that the AICD and Mediator coordinately regulate a neural gene network with direct relevance to AD pathology. To confirm an extend this hypothesis, we propose the following aims: (1) Elucidate the mechanistic basis for coordinate transcriptional control by AICD and Mediator. We will combine RNAi-mediated APP and MED12 depletion with ChIP-exo/seq to render high resolution genome-wide binding profiles for the AICD and its Mediator-dependent epigenetic imprint; (2) Determine the correlative relationship between Mediator-dependent AICD-target gene expression and AD severity. We will investigate pathologic changes in AICD-target gene expression as a course of AD using histologically staged postmortem brain tissues from AD patients and an established mouse model of AD. Statistical analyses will be used to establish whether AICD-target gene expression may be correlated with disease severity. We expect these studies to have important basic and translational implications for AD.

Further information available at:

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