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Abstract

Characterization of the Role of the Metalloproteinase ADAM17 in Alzheimer's Disease

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ADAM17 is a transmembrane metalloprotease with protein cleavage activity. As an alpha-secretase, ADAM17 plays a role in the processing of the amyloid precursor protein (APP). Cleavage of APP in the amyloidogenic pathway leads to the production of amyloid beta (Aβ). However, in the alternative non-amyloidogenic pathway involving ADAM17, no Aβ is formed. Furthermore, a product of this alternative pathway is believed to protect neurons by regulating Aβ levels. Decreased ADAM17 activity could thus contribute to the accumulation of Aβ plaques in Alzheimer's disease (AD). Recently, a heterozygous ADAM17 R215I mutation has been implicated in familial late-onset AD. ADAM17 was also associated with Alzheimer's pathology in a GWAS study, but a clear mechanistic understanding is missing. This project aims to delineate cortical neuron characteristics derived from human iPS cells with wildtype ADAM17 and heterozygous R215I mutated ADAM17. The R215I mutation, located in ADAM17's prodomain—essential for protein maturation and trafficking—likely disrupts membrane localization and proteolytic activity, potentially exacerbating Aβ aggregation and Alzheimer's progression. Given ADAM17's broad substrate spectrum, encompassing over 90 proteins with diverse functions, the dysregulation of ADAM17 could profoundly influence cellular development, differentiation, adhesion, signalling, survival and inflammation. Uncovering the mechanism of ADAM17 dysfunction would offer insights into Alzheimer's complex aetiology.