THE PROTEIN KINASE DYRK1A INCREASES ALPHA-SECRETASE ACTIVITY IN NEURONAL CELLS AND ACCELERATES ALPHA-CLEAVAGE OF AMYLOID PRECURSOR PROTEIN

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The high prevalence of Alzheimer disease (AD)-like pathology, e.g. β-amyloidosis, in adults with Down syndrome (DS) has been attributed to the extra copy of the gene encoding amyloid precursor protein (APP). Another gene present as triplicate in DS encodes the protein kinase DYRK1A. Recent reports show that DYRK1A phosphorylates APP and enhances its cleavage by β-secretase and γ-secretase and the production of Aβ peptides. In contrast, α-secretases cleave APP within the β-amyloid sequence and counteract Aβ toxicity.

This study addresses the question whether DYRK1A affects the processing of APP by α-secretase activity.

The α-secretase activity of cultured cells was measured in cell lysates using a fluorogenic peptide-based substrate mimicking the α-cleavage site of APP. Surface expression of ADAM10/17 was determined using flow cytometric analysis. APP processing was detected with an antibody directed against the extracellular domain.

Activity of α-secretases was enhanced when DYRK1A was overexpressed in neuronal PC12 cells. This upregulation was markedly suppressed using specific inhibitors against the metalloprotease ADAM17 or DYRK1A and was not seen with kinase inactive DYRK1A. Mechanistically, upregulation of α-secretase activity by DYRK1A was distinct from the phorbol ester-induced activation of α-secretase and was associated with increased surface expression of ADAM17 but not ADAM10. Finally, cleavage of endogenous APP in human neuroblastoma cells was enhanced by overexpression of DYRK1A and suppressed by inhibition of ADAM17 or DYRK1A.

These results demonstrate a link between DYRK1A activity and cleavage of APP via ADAM17, suggesting that DYRK1A may switch on protective pathways potentially limiting β-amyloid production.