IDENTIFICATION OF TRANSCRIPTION FACTORS MODULATING GENE-EXPRESSION OF ALZHEIMER’S DISEASE RELATED PROTEINASES ADAM10 AND BACE1

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A pivotal event during the pathogenesis of Alzheimer’s Disease (AD) is the proteolytic cleavage of the amyloid precursor protein (APP) by the β-secretase BACE1 (beta-site APP cleaving enzyme1). This proteolysis leads to generation of neurotoxic Aβ-peptides, which are the major components of AD-characteristic amyloid plaques. Alternatively, APP can be cleaved by the α-secretase ADAM10 (a disintegrin and metalloproteinease10) whereby the formation of Aβ-peptides is prevented. In addition, the neuroprotective cleavage product sAPPα is generated. Unravelling physiological contexts, in which a misbalance of gene expression of both proteinases emerges, might contribute to a deeper understanding of AD-pathogenesis.

For this approach we established a bivalent luciferase reporter assay for the human promoters of ADAM10 and BACE1. Initially, we performed a screening of 704 human transcription factors (TFs) by retro-cotransfection of reporter plasmids together with TF-cDNAs in human neuroblastoma cells. 49 TFs significantly modulated the ratio of ADAM10 to BACE1 transcriptional activity and were subsequently classified according to their expression levels in the CNS of adults. The remaining 24 factors were tested by reporter gene assays for their ability to influence gene expression of the substrate APP itself: 15 TFs displayed common regulatory mechanisms regarding proteinase and substrate expression. Additionally, we analysed the expression of candidate TFs in hippocampal nuclear protein extracts of AD-patients versus a normal aged control. This should indicate which TFs contribute to a putative defective regulation of ADAM10 and BACE1 gene expression during AD-pathogenesis and might bear new therapeutic targets.