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MicroRNA-4422-5p as a negative regulator of Amyloidogenic Secretases: A Potential biomarker for Alzheimer's disease

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Beta-secretase (BACE1) and Gamma-Secretase Activating Protein (GSAP) are pivotal enzymes in the cleavage of Amyloid Precursor Protein (APP). Beta-amyloid (Aß) formation is considered one of the main reasons for Alzheimer's disease (AD) pathology. In our preliminary study, a series of microRNAs (miRs) with possible interaction with BACE1 and/or GSAP was selected using computational analysis. Our results showed that miR-4422-5p had a reduced level in the serum of AD patients. In this study, the effect of miR-4422-5p using miR-4422-5p mimic and inhibitor on BACE1 and GSAP were investigated, and a probable novel early diagnostic marker for AD was introduced. The effect of miR-4422-5p interaction with BACE1 and GSAP was evaluated via in vitro experiments using dual-luciferase assays, western blotting, and Immunocytochemistry. Luciferase assay demonstrated that miR-4422-5p mimic suppresses BACE1 and GSAP expression by directly targeting the 3'UTR of BACE1 and GSAP mRNA in HEK293T cells. Also, western blotting and immunocytochemistry confirmed the regulatory role of miR-4422-5p mimic on BACE1 and GSAP genes. miR-4422-5p mimic significantly decreased BACE1 and GSAP protein expression in SH-SY5Y and A549 cells, respectively. Moreover, miR-4422-5p-inhibitor reversed the expression processes in both cell lines. Our data suggest that miR-4422-5p may be an important regulator of both BACE1 and GSAP genes and can represent a novel potential biomarker or therapeutic target in AD.

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