Understanding APP Metabolism

The Transcriptionally Active Amyloid Precursor Protein (APP) Intracellular Domain Is Preferentially Produced from the 695 Isoform of APP in a β-Secretase-dependent Pathway

Processing of the amyloid precursor protein (APP) by β- and γ-secretases generates several biologically active products, including Alzheimer disease-associated amyloid-β (Aβ) fragments and the APP intracellular domain (AICD), which regulates transcription of several neuronal genes, including the Aβ-degrading enzyme neprilysin (NEP). Through alternative splicing, APP can exist in three primary isoforms: APP<sub>695</sub>, APP<sub>751</sub>, and APP<sub>770</sub>. An important research goal of this still mysterious protein is to understand how each isoform contributes to the generation of APP metabolites, and this topic is examined in this Paper of the Week. Nikolai Belyaev and colleagues expressed each major isoform in neuronal cells and found that only APP<sub>695</sub> up-regulated AICD and NEP expression, which also resulted in increased levels of Aβ<sub>1-40</sub> and Aβ<sub>1-42</sub> fragments. Chromatin immunoprecipitation showed that AICD was associated with the NEP promoter in APP<sub>695</sub> cells, whereas histone deacetylase 1 occupied the promoter in APP<sub>751</sub> and APP<sub>770</sub> cells. Increased NEP expression could be abolished in APP<sub>695</sub> cells by β- or γ-secretase inhibitors (but not an α-secretase inhibitor), as well as by cholesterol depletion. Together, these results could help researchers selectively manipulate Aβ fragments and other APP metabolites and be useful in the development of Alzheimer disease therapeutics.

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