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Commentary

Overlapping the Variable Contributions of the Amyloid Precursor Protein (APP) Gene Expressions in Neurological Activity

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DESCRIPTION

The APP gene family consists of three members in mammals: Amyloid Precursor Protein (APP), Amyloid Precursor-Like Protein 1 (APLP1) and Amyloid Precursor-Like Protein 2 (APLP2). These proteins share a similar modular domain structure and are type I transmembrane glycoproteins that can be cleaved by secretases to generate various peptides with diverse functions. The most studied member of the APP gene family is APP, which is implicated in Alzheimer 's disease (AD), a neurodegenerative disorder characterized by the accumulation of Amyloid Beta (Aβ) plaques and neurofibrillary tangles in the brain. Aβ is a peptide derived from the sequential cleavage of APP by β- and γ-secretases. However, APP can also be processed by α-secretase, which prevents Aβ formation and generates soluble APPα (sAPPα), a neuroprotective peptide that promotes neuronal survival, differentiation, synaptogenesis and plasticity.

The physiological functions of APLP1 and APLP2 are less clear, but they are likely to have overlapping and distinct roles from APP. APLP1 and APLP2 can also be cleaved by secretes to produce soluble peptides that may modulate the activity of other proteins or receptors. For example, sAPLP2 has been shown to inhibit platelet aggregation by binding to glycoprotein Ibα, a component of the von Wille-brand factor receptor. APLP1 and APLP2 can also form heterodimers with APP and regulate its processing and trafficking. The APP gene family is widely expressed in various tissues and organs, but it is particularly abundant in the nervous system, where it plays important roles in neuronal development, function and maintenance. Studies using knockout mice have revealed that the APP gene family is essential for normal brain development and synaptic function. Mice lacking APP or APLP2 die perinatally due to severe defects in neuromuscular junction formation and synaptic transmission. Mice lacking both APP and APLP2 exhibit embryonic lethality due to impaired neural tube closure and brain haemorrhage. Mice lacking APLP1 show impaired spatial learning and memory, as well as reduced synaptic plasticity.

The APP gene family is also involved in neuronal signaling and communication. The peptides derived from the APP gene family can bind to various receptors and modulate their activity. For example, sAPPα can bind to the low-density Lipoprotein Receptor-Related Protein 1 (LRP1) and activate downstream signalling pathways that promote neuronal survival and plasticity3. Aβ can bind to several receptors, such as the Receptor for Advanced Glycation End Products (RAGE), the N-Methyl-D-Aspartate Receptor (NMDAR) and the α7 nicotinic Acetylcholine Receptor (α7nAChR), and induce neurotoxicity, inflammation and oxidative stress. The APP gene family also participates in cell adhesion, migration and axon guidance. The extracellular domains of the APP gene family can interact with various extracellular matrix proteins, such as heparin sulphate proteoglycans, lamina, collagen and integrin's, and mediate cell-cell or cell-matrix interactions. The intracellular domains of the APP gene family can interact with various cytoskeletal proteins, such as tubulin, actin, kinetin and dynein, and regulate microtubule dynamics and axonal transport. The APP gene family can also modulate the expression or activity of various guidance molecules, such as netrin-1, semaphorin 3A, ephrin-A5 and slit-2, and influence axon growth and path finding.

In summary, the APP gene family is a multifunctional group of proteins that performs various physiological functions on the surface of neurons and other cells. The peptides derived from the APP gene family have diverse effects on neuronal survival, differentiation, synaptogenesis, plasticity, signalling, communication, adhesion, migration and axon guidance. The dysregulation of the APP gene family or its processing may contribute to the pathogenesis of AD and other neurological disorders.

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