Insights into the Interaction of N-APP with Death Receptor 6 in Inducing Neuronal Apoptosis

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease with a devastating clinical course yet currently lacks an effective treatment method. A recently proposed biochemical model for neuronal damage revolves around on a novel protein-protein interaction between an N-terminal fragment of the amyloid precursor protein (N-APP) and death cell receptor six (DR6) and establishes a framework for understanding AD pathophysiology. To better discern the interactions of N-APP with DR6 and the roles of aberrant metal ions (Cu, Zn) in N-APP-DR6 binding, the interaction mechanism of N-APP with DR6 in mediating neuronal cell apoptosis was studied. To this end, truncated N-APP and DR6 were cloned, expressed and purified. The interaction between N-APP and DR6 was investigated in the presence and absence of copper and zinc ions. Thermodynamic studies indicated that N-APP126 binds with DR6 via hydrophobic interactions with stronger binding between N-APP286 and DR6 than N-APP 126 with DR6 due to the additional acidic region of N-APP286. Furthermore, Cu/Zn can promote the binding between N-APP and DR6, and the binding of N-APP and DR6 promotes neuronal apoptosis, a vital component of AD pathophysiology. These results on the functions of N-APP(18-286) and DR6(41-218) and the underlying binding mechanism directly supplement the design of novel structure-based antagonists in retarding AD progression.

Awards Won:

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