S22-3 Ganglioside cluster-mediated aggregation and cytotoxicity of amyloid beta-peptide: molecular mechanism and inhibition

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The abnormal aggregation of amyloid β-peptide (Aβ) and its deposition to neurons are closely related to the pathogenesis of Alzheimer's disease. We revealed a novel aggregation mechanism in lipid rafts. Aβ recoginzes and binds to ganglioside clusters formed by an increase in cholesterol level. The membrane-bound Aβ forms an α-helix-rich structure at lower densities. At higher densities, Aβ undergoes a conformational transition to a β-sheet-rich structure that can serve as a seed for amyloid fibril formation. The amyloid fibrils are more toxic than those formed in solution, suggesting the existence of polymorphisims in amyloids.

Low molecular weight compound that can inhibit the aggregation process would be candidates for therapeutics agents. We examined the effects of eight compounds on the raft-mediated amyloidgenesis by Aβ. These compounds are known to inhibit amyloidgenesis in solution, Among them, four componds exhibited inhibitory effects. The most potent nordihydroguaiaretic acid prevented Aβ from membrane binding by interacting with Aβ and raft membranes. Aβ formed small elongated particles instead of forming fibrils in the presence of the compound.

< Selected papers > J Biol Chem 276, 24985 (2001); Biochemistry 41, 7385 (2002); J Mol Biol 371, 924 (2007); BBA 1768, 122 (2007); J Mol Biol 382, 1066 (2008).