

Abstract

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Amyloid-beta fibrillogenesis: structural insight and therapeutic intervention.

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BACKGROUND: Structural insight into the conformational changes associated with aggregation and assembly of fibrils has provided a number of targets for therapeutic intervention. Solid-state NMR, hydrogen/deuterium exchange and mutagenesis strategies have been used to probe the secondary and tertiary structure of amyloid fibrils and key intermediates. Rational design of peptide inhibitors directed against key residues important for aggregation and stabilization of fibrils has demonstrated effectiveness at inhibiting fibrillogenesis. Studies on the interaction between Abeta and cell membranes led to the discovery that inositol, the head group of phosphatidylinositol, inhibits fibrillogenesis.

FINDINGS: As a result, scyllo-inositol is currently in clinical trials for the treatment of AD. Additional small-molecule inhibitors, including polyphenolic compounds such as curcumin, (-)-epigallocatechin gallate (EGCG), and grape seed extract have been shown to attenuate Abeta aggregation through distinct mechanisms, and have shown effectiveness at reducing amyloid levels when administered to transgenic mouse models of AD.

CONCLUSION: Although the results of ongoing clinical trials remain to be seen, these compounds represent the first generation of amyloid-based therapeutics, with the potential to alter the progression of AD and, when used prophylactically, alleviate the deposition of Abeta.

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