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Amylin as a Novel Contributor to Alzheimer's Disease and Natural Product Inhibitor Discovery

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Epidemiological studies show significant association between obesity-related type 2 diabetes (T2D) and risk for cerebrovascular disease and dementia (including neurodegenerative Alzheimer's disease, AD). Amylin is a 37-residue peptide hormone that is co-secreted with insulin from pancreatic beta cells. It is a highly amyloidogenic protein, similar to amyloid beta peptide Abeta 42 which is a well-known peptide factor involving in AD in the brain. Recent clinical studies reported that amylin plaques were deposited in the brain of diabetic patients, but not in age-matched health controls. Our cell-based studies demonstrated that amylin amyloid is highly toxic to human and mouse neuronal cell lines SH-SY5Y and Neuro2A. From a targeted screening of a collection of natural compounds used in complementary and alternative medicine, we identified that rosmarinic acid (RA) is a highly potent inhibitor against amylin amyloid formation (estimated to be one to two hundred nM in IC_{50}) and it rescues cell viability from amylin-induced cytotoxicity. Dissecting the two functional groups of rosmarinic acid, we found each group, caffeic acid and salvianic acid A respectively, have weaker-than-RA inhibitory and rescue functions, suggesting an additive effect of the two functional groups. RA can readily break up amylin amyloid in the entire course of fibrillation, reversing the amyloid formation from both thioflavin T fluorescence assay and transmission electron microscopy observations. We demonstrate that rosmarinic acid inhibits amylin amyloid via a site-specific mechanism, conjugating the amine groups in the peptide. Consistent with the experimental results, the inhibition effect by rosmarinic acid is demonstrated in computational molecular simulation analyses, providing an additional mechanism of non-covalent interactions between RA and the peptide as a way to block amylin oligomer and amyloid formation. Additional natural product inhibitor leads will also be discussed.

Biography

Bin Xu received his PhD from Case Western Reserve University in 2004 followed by Postdoctoral studies at Fred Hutchinson Cancer Research Center. Since 2011, he has been a tenure-track Assistant Professor in the Department of Biochemistry and Center for Drug Discovery at Virginia Tech. His research interest concern cell surface receptor-ligand binding, receptor signaling, novel ligand and receptor discovery, and translational structure-based and computer-aided ligand design with applications to novel peptide hormones and natural products relevant to diabetes, obesity, neurodegenerative diseases, and nanomedicine. He has published more than two dozens publications in premier international peer-reviewed journals.

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