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Targeting the toxic oligomers of amyloidogenic proteins by self-assembled cyclic D, L-α-peptides: Potential application for Alzheimer's and Parkinson's diseases

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Protein misfolding and aggregation is the fundamental cause of more than 20 amyloidogenic diseases affecting either the central nervous system or a variety of peripheral tissues. Although peptides and proteins of various sequences can self-assemble into toxic amyloid structures, they share common three-dimensional features that may promote their cross-reaction. Given the significant structural and biochemical similarities between amyloids and the architecture of self-assembled cyclic D, L- α-peptides, we hypothesized that the latter may bind and stabilize the non-toxic forms of different amyloids, thereby preventing their aggregation into toxic forms. By screening an unbiased library of six-residue cyclic D,L-α -peptides and optimizing the activity of a lead peptide, we found one cyclic D, L- α -peptide (CP-2) that interacts strongly with Alzheimer's disease associated Amyloid beta (Aβ) and inhibits its aggregation and toxicity. Further studies including Thioflavin T assays, electron microscopy, and circular dichroism spectroscopy, collectively suggest that CP-2 could also effectively cross-interact with Parkinson's disease associated α-synuclein (α-syn), prevent its aggregation, and remodels its fibrils to non-toxic amorphous species, through an "off pathway" mechanism. NMR studies show that CP-2 interacts with the N-terminal and the non-Aβ component region of α-syn, which are responsible for α-syn's membrane interactions and self-assembly, and so changes its conformation. Dot-blot and cell survival assays suggest that CP-2 reduces the amount of toxic α-syn oligomers and protects PC-12 and SH-SY5Y cells from α-syn induced toxicity. Moreover, CP-2 permeates cells through endosomes/lysosomes, co-localizes with intracellular α-syn and reduces its accumulation and toxicity in neuronal cells over-expressing α-syn. Our studies suggest that targeting the common structural conformation of amyloids may be a promising approach for developing new therapeutics for amyloidogenic diseases.

Biography

Shai Rahimipour has received his Bachelor's degree in Chemistry from Bar-Ilan University, Ramat-Gan, Israel in 1993 and his Doctorate in Organic Chemistry and Neurobiology from the Weizmann Institute of Science in 2001. After Full bright and HFSP Postdoctoral Fellowships at the Scripps Research Institute, La Jolla, CA, he began his independent academic career in 2006 at the University of Bar-Ilan, where he is currently a Professor of Chemistry. His research program focuses on utilizing self-assembling systems to study the aggregation mechanism of amyloids and to explore their properties to induce multi-valency.

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