Spring 2022

Repurposing human α-defensin 6, an antimicrobial peptide, as a beta amyloid inhibitor

Eleanor Plaster
emp86@uakron.edu

Revised Executive Summary

Alzheimer's disease (AD), experienced worldwide by around 50 million people, is the most common neurodegenerative disease. While the pathological mechanism of AD remains unclear, it is well accepted that the "amyloid cascade hypothesis" is one of the most significant causes of AD. Therefore, many beta amyloid (Aβ) inhibitors, including small organic molecules, nanoparticles, polymers, and mimetic peptides, have been developed to interfere with Aβ aggregation. However, none of these Aβ inhibitors have successfully passed clinical trials because of their low efficiency, difficulties crossing the blood-brain barrier, low biocompatibility, and high toxicity. Therefore, in this work, a "like interacts with like" hypothesis was proposed to discover peptide-based Aβ inhibitors with a β-sheet motif. Compared with other types of Aβ inhibitors, peptide-based Aβ inhibitors possess several intrinsic advantages including good biocompatibility, ease of synthesis and modification, controllable folding structures, and high binding affinity to targets. From a structure viewpoint, due to the conformationally similar β-sheet motifs, Aβ and inhibitors are likely to interact with each other to form non-toxic Aβ-inhibitor aggregates, thus preventing Aβ-Aβ self-interaction.

Considering that (1) human α-defensin 6 (HD-6) is an intestinal defensin that is made by intestinal Paneth cells, making communication between the brain and intestines possible via the gut-brain axis; (2) HD-6 is a cationic peptide that is able to electrostatically interact with Aβ; and (3) HD-6 contains β-sheet segments, which is essential to interact with Aβ via the "like interacts with like" hypothesis, HD-6 was repurposed to study its ability to act as a Aβ inhibitor.

Collective data from Thioflavin T (ThT) assays, circular dichroism (CD) spectroscopy, and atomic force microscopy (AFM) showed that HD-6 exhibited surprising inhibition ability by slowing the Aβ aggregation rate, delaying secondary structure transition, and reducing Aβ fibril formation. In addition, cell assays including lactate dehydrogenase (LDH) assays and 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays suggested that HD-6 can protect neurons from Aβ-induced toxicity. These findings therefore indicate the potential role of HD-6 as a promising therapeutic agent for the prevention and treatment of AD.