Double-blocking Anti-crosslinking Strategy for AD Drug Development

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Research Abstract

? DESCRIPTION (provided by applicant): Amyloid beta (Aß) peptides are highly hydrophobic substances, and they are very prone to aggregate under a biologically relevant environment or under mimicked conditions. According to the literatures, there are two primary processes for the

aggregation: physical stacking and crosslinking of Aßs. The former process is due to the hydrophobicity of Aßs, and is reversible. The crosslinking process can be induced by metal ions (copper, zinc, iron, etc) and other factors (such redox reaction), and the crosslinked Aßs are irreversibly aggregated, and could not be dissociated with detergents. Irreversible crosslinked Aßs are considerably resistant to degradating by enzymes and singnifciantly contribute to the Aß pathology. Therefore anti-crosslinking strategy can be an effective approach for AD drug discovery. When metal ions induce crosslinking of Aßs, redox reactions also normally occur consequentially. This indicates that blocking the harmful effects caused by both metal ions and redox reaction should be considered for compound designing. For copper induced crosslinking, copper first coordinates with H13 and H14 of Aßs, and then initialize an oxidation reaction to generate H2O2, which consequentially oxidize tyrosine (Y10) to finally lead to crosslink Aßs. Obviously, double-blocking is very necessary for a potential effective drug. In our previous studies we synthesized curcumin analogues that can bind to Aßs, and specifically interact with H13 or H14 of Aß peptides. In this application, we propose a double-blocking anti-crosslinking strategy, in which curcumin scaffold is specifically engaged with Aßs, and imidazole/pyrazole/triazole moiety competes copper coordination of H13 and H14, and phenol moiety is placed around tyrosine (Y10) as a scapegoat for the oxidation of Y10. Our design will allow us to position the right weapons at the right places, thus to efficiently inhibit the crosslinking. Finally therapeutic efficacy of the optimized candidates will be evaluated in vivo using molecular imaging technologies developed in our group.

Further information available at:

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