Carbazole-based Cyanine as a Versatile Diagnostic Probe and Effective Treatment Drug for Alzheimer's Disease

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Abstract:
Alzheimer's disease (AD) is the most prevalent neurodegenerative dementia. Currently, there is still no drug that can cure AD and the underlying cause is also not well understood, which poses a grand challenge for the development of effective diagnostic tools and treatment for this devastating disease. Amyloid-β (Aβ) plaque, being one of the important pathological hallmarks in an AD brain, has become an important biomarker and target of the disease. We present here a multifunctional theranostic cyanine, which exhibits good Aβ oligomer selectivity with a high binding affinity, attributed to the synergistic effect of strong π-π stacking and intermolecular CH/O and CH/F interactions. Because of its excellent blood–brain barrier (BBB) penetrability and low bio-toxicity, the in vivo application in labelling Aβ oligomers was successfully demonstrated in 7 month-old APP/PS1 double Tg and APP/PS1/Tau triple Tg mouse models. In addition, this cyanine shows remarkably effective inhibition against Aβ aggregation and highly desirable neuroprotective effects against Aβ-induced toxicity, including the inhibition of ROS production and Ca^{2+} influx. Most importantly, it has been found to exhibit effective in vivo therapeutic efficacy for the treatment of multiple neuropathological changes in 5XFAD and 3XTg-AD mouse models. It significantly reduces not only the levels of Aβ oligomers, tau aggregates and plaques but also the levels of amyloid precursor protein (APP) and its metabolites via autophagy lysosomal degradation pathway (ALP) in the brains of AD mice. It also reduces astrocyte activation and microgliosis ultimately alleviating neuro-inflammation. Furthermore, it mitigates hyperphosphorylated tau aggregates, synaptic deficits and ameliorates synaptic memory function, and cognitive impairment in AD mouse models. The mechanistic studies have shown that this cyanine promotes ALP and lysosomal biogenesis for the clearance of soluble, insoluble Aβ, and phosphorylated tau. Our results unambiguously demonstrate effective etiological capabilities of this theranostic cyanine to target and intervene multiple neuropathological abnormalities in AD mouse models. The findings of this study could lead to important advancements in AD drug development.