CLEARANCE OF AMYLOID-BETA IN ALZHEIMER'S DISEASE

To understand the pathogenesis and develop potential therapies in animal models

A THESIS SUBMITTED IN TOTAL FULFILMENT
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THESIS SUMMARY

Alzheimer's disease (AD) is the most common cause of dementia. No strong disease-modifying treatments are currently available. Amyloid-beta peptide (Aβ) appears to play a pivotal role in the pathogenesis of AD. We focused our interest on revealing the pathogenesis of the disease and developing novel therapeutic modalities. The thesis consists of three projects:

1. Prevention of AD by intramuscular delivery of an anti-Aβ single chain antibody (scFv) gene

Immunotherapy is effective in removing brain Aβ, but was associated with detrimental effects. In the present study, the gene of an anti-Aβ scFv was delivered in the hind leg muscles of APPSwe/PS1dE9 mice with adeno-associated virus at three months of age. Six months later, we found that brain Aβ accumulation, AD-type pathologies and cognitive impairment were significantly attenuated in scFv-treated mice relative to enhanced green fluorescence protein (EGFP)-treated mice. Intramuscular delivery of scFv gene was well tolerated by the animals. These findings suggest that peripheral application of scFv is effective and safe in preventing the development of AD, and would be a promising non-inflammatory immunological modality for prevention and treatment of AD.

2. Prevention of AD with grape seed derived polyphenols

Polyphenols extracted from grape seeds are able to inhibit Aβ aggregation, reduce Aβ production and protect against Aβ neurotoxicity *in vitro*. We investigated the therapeutic effects of a polyphenol-rich grape seed extract (GSE) in vivo.

APPSwe/PS1dE9 transgenic mice were fed with normal AIN-93G diet (control diet), AIN-93G diet with 0.07% curcumin, or diet with 2% GSE beginning at 3 months of age for 9 months. Total phenolic content of GSE was 592.5 mg/g dry weight, including gallic acid, catechin, epicatechin and proanthocyanidins. Long-term feeding of GSE diet was well tolerated. The Aβ levels in the brain and serum of the mice fed with GSE were reduced by 33% and 44% respectively compared with the mice fed with the control diet. Amyloid plaques and microgliosis in the brain of mice fed with GSE were also reduced by 49% and 70% respectively. In conclusion, polyphenol-rich GSE is promising to be a safe and effective drug to prevent the development of AD.

3. Roles of p75NTR in the development of AD

P75NTR has been suggested to mediate Aβ induced neurotoxicity. However, its role in the development of AD is undetermined. APPSwe/PS1dE9 transgenic mice were crossed with p75NTR knockout mice to generate APPSwe/PS1dE9 mice with p75NTR gene deleted. P75NTR mainly expressed in the basal forebrain neurons and degenerative neurites in neocortex and hippocampus. Genetic deletion of p75NTR gene in APPSwe/PS1dE9 mice reduced soluble Aβ levels, but increased the insoluble Aβ accumulation and Aβ plaque formation in the brain. P75NTR deletion decreased Aβ production of cortical neurons *in vitro*. Recombinant extracellular domain of p75NTR attenuated the oligomerization and fibrillation of synthetic Aβ42 peptide *in vitro*, and reduced local Aβ plaques after hippocampus injection *in vivo*. Our data suggest that p75NTR plays an important role in AD development and may be a valid therapeutic target for the treatment of AD.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

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PERSONAL PUBLICATIONS AND CONFERENCE PRESENTATIONS

Refereed journal articles

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2. **Wang YJ**, Gao CY, Yang M, Pollard A, Valadares D, Liu XH, Dong XY, Wu XB, Zhong JH, Zhou HD, Zhou XF (2010). Intramuscular delivery of a single chain antibody gene prevents brain Abeta deposition and cognitive impairment in a mouse model of Alzheimer's disease. Brain Behav Immun (in revision).
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1. **Wang YJ**, Thomas P, Zhong JH, Bi FF, Kosaraju S, **Pollard A**, Fenech M, Zhou XF. (2008) Consumption of polyphenol-rich grape seed extract prevents amyloid deposition and suppresses inflammation in the brain of a transgenic mouse model for AD. Society for Neuroscience (SfN) 38th annual meeting, Washington DC, US, Nov19 (Symposium talk)
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3. **Wang YJ**, Pollard AN, Zhou HD, Zhong JH, and Zhou XF. (2006) Characterization of an AD Mouse Model Bearing Mutant Genes of Amyloid Precursor Protein and Human Presenilin 1. Australian Neuroscience Society (ANS) 26th annual meeting, Sydney, Australia, Jan 31-Feb 3. (Poster presentation)

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