Commentary   **Open Access**

Bidirectional Regulation of A beta Aggregates: Focus on Therapeutic Targets for Alzheimer's Disease

Ying Zhang*, and Jiang-Tao Li

College of Life Sciences and Bioengineering, Beijing Jiaotong University, Beijing 100044, P.R China

***Corresponding author:** Ying Zhang, College of Life Sciences and Bioengineering, Beijing Jiaotong University, Beijing 100044, P.R China, Tel: 86-10-51684351-201; Fax: 86-10-51683887, E-mail: yingzhang@bjtu.edu.cn

Commentary

Alzheimer disease (AD) is the most prevalent dementia of aging adult, characterized by progressive amyloid aggregates in the brain and impairment in cognition and memory. In recent year, data from clinical trials and mouse models showed that Aβ immunotherapy had brought new hopes to AD treatment, although undesirable side effects occurred during the course of clinical trials based on Aβ targeting antibody drugs. Our previous study showed that single chain fragment variable (scFv) played key roles in ultrastructural regulation of Aβ fibrillogenesis and disaggregation. In this invited commentary, bidirectional regulation of Aβ aggregates would be discussed as one of the methods for further study in AD treatment.

Single Chain Fragment Variable (scFv)

The blood-brain barrier (BBB) limits brain uptake of antibodies [1], which will reduce the drug effect to some extent. The scFvs are usually produced by fusing the variable regions of the antibody heavy (VH) and light chains (VL), creating a much smaller protein with unaltered specificity to antigens. Because of its small size, scFvs are much easier to be delivered into the brain. The formula weight of the scFv is about only one fifth of Immunoglobulin G (IgG) [2], which would apply to go through the BBB. Therefore, the advantage of elevated concentrations of scFv in the brain may increase the inhibition of Aβ aggregation. The first anti-Aβ scFv was produced by Frenkel *et al.* based on the variable regions of an anti-Aβ IgM 508 antibody [3].

Single chain antibodies can be used to avoid antibody-dependent cell-mediated cytotoxicity (ADCC) and increase the safety of AD immunotherapy. VH and VL domains form the antigen binding region, and the Fc fragment is not necessary for Aβ immunotherapy. Therefore, the size of entire drug molecules decrease and the side effects induced by Fc fragment should be avoided if the VH and VL are enough to control Aβ aggregates.

Next step, alternative engineered antibodies can be developed on the basis of single chain antibodies. The side effects of Aβ immunotherapy, such as meningoencephalitis, vasogenic edema or cerebral microhemorrhages, might also be avoided by novel forms of antibodies including Fc-engineered antibodies, single domain antibodies, intrabodies, and bispecific antibodies.

Bidirectional Regulation of Amyloid Formation

The Aβ aggregation in the brain has been considered as the leading cause in the pathogenesis of AD. Our data [2] suggested that the scFv forms of monoclonal antibody consisting of VH, linker peptide, and VL could inhibit Aβ aggregation and fibril elongation. This study is the first to investigate the bidirectional regulation of the function of Aβ

aggregation through anti-Aβ scFv based on the ultrastructural changes.

Aβ aggregates can be blocked by an anti-Aβ scFv with the amino terminal (1-6) epitope, although conformations of carboxyl terminal peptide are necessary for fibril formation. The underlining mechanism of the N-terminus of scFv influence whole molecule aggregation remains unclear. However, this reminds that drugs modifying the structures of Aβ42 N termini can be used in AD immunotherapy.

Emphasizing on AD Prevention

Prevention is much more important in AD treatment. In recent clinical trials, bapineuzumab and solanezumab targeting Aβ have been reported not to improve the cognitive disable in mild to moderate AD patients. Antibodies that block Aβ aggregation may be used to delay the onset of disease without clinical symptoms. Therefore, the antibodies target should be in early-AD. Our data showed that [2] in the *in vitro* cell-free system, the effect of this scFv was substantially significant when used during the initiation stage of Aβ aggregation, which could be helpful in further AD prevention study.

On the basis of the diameter of Aβ oligomers and the length of the Aβ fibrils, the on-pathway Aβ aggregation model can be used to investigate the mechanisms of Aβ fibrillogenesis and to find out the inhibitors of Aβ aggregation. Furthermore, monomer nucleation can be employed to imitate early stage of Aβ aggregation in AD. Therefore, the "window" of the period of nucleation can be the correct target for AD prevention.

Common Mechanism for Protein Misfolded Disorders (PMDs)

In our previous study, we developed single chain variable fragments against Abeta and evaluated their effects on the fibrillogenesis and disaggregation of Abeta. We found that the scFv produced in baculovirus and *E. coli* expression systems have a similar effect, which not only inhibit the Abeta fibril elongation but also disassemble the mature Abeta fibril *in vitro*. The scFvs showed an encouraging effect *in vitro*. This is an interesting study with a broader interest for researchers of not only Alzheimer's disease, but also of other neurodegenerative diseases. In the past decade, scFv-based immunotherapies have been reported to target various forms of protein aggregates including Aβ, SNCA, Htt, and PrP proteins [4]. A novel 2N tau isoform-specific scFv have been identified for experiment in a tau transgenic mouse model [5,6].

Taken together, scFv-based *in vitro* regulation of Aβ aggregates provided valuable insight into the ultrastructural changes of Aβ

aggregation and the prevention and therapeutic strategies for Aβ targeting immunotherapy in AD.

Acknowledgments

References

1.   Bien-Ly N, Boswell CA, Jeet S, Beach TG, Hoyte K, et al. (2015) Lack of Widespread BBB disruption in Alzheimer's disease models: focus on therapeutic Antibodies. Neuron 21: 289-97.

2.   Zhang Y, Yang HQ, Fang F, Song LL, Jiao YY, et al. (2015) Single chain variable fragment against aß expressed in baculovirus inhibits abeta fibril elongation and promotes its disaggregation. PLoS One 10: e0124736.

3.   Frenkel D, Solomon B, Benhar I (2000) Modulation of Alzheimer's beta-amyloid neurotoxicity by site-directed single-chain antibody. J Neuroimmunol 106: 23-31.

4.   Zuber C, Knackmuss S, Rey C, Reusch U, Röttgen P, et al. (2008) Single chain Fv antibodies directed against the 37 kDa/67 kDa laminin receptor as therapeutic tools in prion diseases. Mol Immunol 45: 144-51.

5.   Nisbet RM, Van der Jeugd A, Leinenga G, Evans HT, Janowicz PW, et al. (2017) Combined effects of scanning ultrasound and a tau-specific single chain antibody in a tau transgenic mouse model. Brain.

6.   Nisbet RM, Polanco JC, Ittner LM, Götz J (2015) Tau aggregation and its interplay with amyloid-Î². Acta Neuropathol 129: 207-220.