From Protein Misfolding to Translational Medical Research for Alzheimer's Disease and ALS

從蛋白質錯誤摺疊到阿茲海默症及漸凍人之轉譯醫學研究

Yun-Ru (Ruby) Chen

陳韻如

[1]*The Genomics Research Center, Academia Sinica, Taipei, Taiwan*

Inclusions attributed from protein misfolding were observed in nearly all neurodegenerative diseases. The inclusions are often characterized as amyloids comprising amyloid fibrils. Amyloid formation is initiated by protein misfolding followed by self-association to ultimately form amyloid fibrils with cross-β spines. The discovery of toxic pre-fibrillar oligomers underscores the importance of understanding the formation of amyloid oligomers and its role in fibrillization. Here, I will first present our recent research focuses on the effects of N-terminal mutation and Zn ion on amyloid-β (Aβ) in Alzheimer's disease (AD) and the inhibitor development. Secondly, I will present our discovery of TDP-43 oligomers and generation of oligomer specific antibodies for diagnostic and therapeutic development. TDP-43 proteinopathies include frontotemporal lobar dementia (FTLD), amyotrophic lateral sclerosis (ALS), and AD. The structural properties of TDP-43 aggregates and their relationship to the pathogenesis are still ambiguous. Here, we demonstrated that the recombinant full-length human TDP-43 forms structurally stable, spherical oligomers that share common properties with amyloid oligomers. Such oligomers are present in the forebrain of transgenic TDP-43 mice and FTLD-TDP patients. In addition, animal studies showed that our oligomer specific antibody is able to rescue motor dysfunction in ALS mice model. The results suggest TDP-43 oligomers play a role in TDP-43 pathogenesis and potentiate the translational application of the antibody.

References:

1. Ling-Hsien Tu et. al., Jim-Min Fang,* and **Yun-Ru Chen***. Rationally Designed Divalent Caffeic Amide Inhibits Amyloid-β Fibrillization, Induce Fibril Dissociation, and Ameliorate Cytotoxicity. **European Journal of Medicinal Chemistry**. 158: 393-404 (2018)
2. Ming-Che Lee et al. and **Yun-Ru Chen***. Zinc ion rapidly induces toxic, off-pathway amyloid-β oligomers distinct from amyloid-β derived diffusible ligands in Alzheimer's disease. **Scientific Reports** 8, Article number: 4772 **(2018)**
3. Tien-Wei Lin et al. and **Yun-Ru Chen***. Alzheimer's Amyloid-β A2T Variant and its N-terminal Peptides Inhibit Amyloid-β Fibrillization and Rescue the Induced Cytotoxicity. **PLoS One**. 12(3):e0174561 **(2017)**

4. Patricia F. Kao, **Yun-Ru Chen**, et al. and Lee-Way Jin*. Detection of TDP-43 oligomers in frontotemporal lobar degeneration-TDP. **Annals of Neurology**, 78(2):211-21. **(2015)**
5. Yu-Sheng Fang et. al., and **Yun-Ru Chen***. "Full-Length TDP-43 Forms Toxic Amyloid Oligomers that are Present in Frontotemporal Lobar Dementia-TDP Patients." (*corresponding author) **Nature Communications,** 5:4824 **(2014)**