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### The development of ErbB2-targeted therapy for Alzheimer's disease

$\gamma$ -Secretase-catalyzed production of amyloid- $\beta$  ( $A\beta$ ) underlies the pathogenesis of Alzheimer's Disease (AD). To identify genetic modifiers that can selectively affect  $\gamma$ -secretase cleavage of APP while sparing Notch cleavage, we generated cell-based assays employing Bioluminescence Resonance Energy Transfer (BRET) technology to monitor the protein-protein interactions between PS1 and two  $\gamma$ -secretase substrates, APP C-terminal fragment (C99) and extracellular domain truncated Notch (N $\Delta$ E). An RNAi screen identified 14 candidate genes whose down-regulation resulted in a selective decrease in the interaction between PS1 and C99. Among those 14 candidate genes, an *ErbB2*-centered interaction network was found to preferentially govern the proteostasis of APP-C99. We further demonstrated that overexpression of *ErbB2* up-regulates the levels of C99 and AICD effectively. The knockdown of *ErbB2* selectively decreased the protein levels of C99, AICD and secreted  $A\beta$  40, but not those of N $\Delta$ E and NICD. Selective suppression of *ErbB2* expression by CL-387,785, an *ErbB1/2*-selective irreversible tyrosine kinase inhibitor, can preferentially attenuate the levels of C99 and AICD, resulting in a significant reduction in  $A\beta$  production. Down-regulation of *ErbB2* by CL-387,785 also resulted in a significant decrease in the levels of C99 and secreted  $A\beta$  in both zebrafish and mouse models of AD, through the activation of autophagy. Oral administration of CL-387,785 for 3 week significantly improves the cognitive functions of APP/presenilin-1 (PS1) transgenic mice. These findings unveil a non-canonical function of *ErbB2* in modulating autophagy and established *ErbB2* as a novel therapeutic target for AD.

### Biography

Yung-Feng Liao has completed his PhD in Biochemistry and Molecular Biology from University of Georgia, Athens, Georgia, USA and Postdoctoral studies from Harvard Medical School/Massachusetts General Hospital/Brigham and Women's Hospital, Boston, Massachusetts, USA. He is the Principal Investigator of the Laboratory of Molecular Neurobiology in the Institute of Cellular and Organismic Biology, Academia Sinica, a premier research institution in Taiwan. He has published more than 50 papers in reputed journals and has been serving either as an Editorial Board Member or as a Peer Reviewer of prestigious journals.

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