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

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γSecretase catalyzed production of Amyloid-β (Aβ) underlies the pathogenesis of Alzheimer's Disease (AD). The aim is to identify genetic modifiers that can selectively affect γ-secretase cleavage of Alzheimer's disease amyloid protein precursor i 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 γ-secretase substrates, Alzheimer's disease amyloid protein precursor i C-terminal fragment (C99) and extracellular domain truncated Notch (NΔE). An RNAi screen identified 14 candidate genes whose downregulation 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 upregulates the levels of C99 and AICD effectively. The knockdown of ErbB2 selectively decreased the protein levels of C99, AICD, and secreted Aβ40 but not those of NΔE 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 Aβ production. Down-regulation of ErbB2 by CL-387,785 also resulted in a significant decrease in the levels of C99 and secreted Aβ in both zebrafish and mouse models of AD, through the activation of autophagy. Oral administration of CL-387,785 for 3 weeks significantly improves the cognitive functions of APP/presenilin-1 (PS1) transgenic mice. These findings unveil a noncanonical 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 and Postdoctoral studies from Harvard Medical School/ Massachusetts General Hospital/Brigham and Women's Hospital. He is the Principal Investigator of the Laboratory of Molecular Neurobiology in the Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan. He has published more than 50 papers in reputed journals and has been serving as an Editorial Board Member and as a Peer Reviewer of prestigious journals.

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