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ERBB2 REGULATES AUTOPHAGIC FLUX TO MODULATE THE PROTEOSTASIS OF APP-CTFS IN ALZHEIMER'S DISEASE

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Proteolytic processing of amyloid precursor protein (APP) C-terminal fragments (CTFs) by γ-secretase underlies the pathogenesis of Alzheimer's disease (AD). An RNA interference screen using APP-CTF [99-residue CTF (C99)] and Notch-specific γ-secretase interaction assays identified a unique ErbB2-centered signaling network that was predicted to preferentially govern the proteostasis of APP-C99. We then found that ErbB2 effectively suppressed autophagic flux by physically dissociating Beclin-1 from the Vps34–Vps15 complex independent of its kinase activity. Down-regulation of ErbB2 by CL-387,785 decreased the levels of C99 and secreted amyloid-β in cellular, zebra fish and mouse models of AD, through the activation of autophagy. Oral administration of an ErbB2-targeted CL-387,785 for 3 weeks significantly improves the cognitive functions of APP/PS1 transgenic mice. This work unveils a non-canonical function of ErbB2 in modulating autophagy and establishes 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 Post-doctoral 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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