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

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ɣ-Secretase catalyzed production of Amyloid. underlies the pathogenesis of Alzheimer's Disease (AD). The aim is to identify genetic modifiers that can selectively affect-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-secretase substrates, Alzheimer's disease amyloid protein precursor I C-terminal fragment (C99) and extracellular domain truncated Notch .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 A?40 but not those of N??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? production. Down-regulation of ErbB2 by CL-387,785 also resulted in a significant decrease in the levels of C99 and secreted A? 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.

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. Consistently, significantly elevated levels of ErbB2 were confirmed in the hippocampus of human AD brains. 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, zebrafish, and mouse models of AD, through the activation of autophagy. Oral administration of an ErbB2-targeted CL-387,785 for 3 wk significantly improves the cognitive functions of APP/presenilin-1 (PS1) transgenic mice. This work unveils a noncanonical function of ErbB2 in modulating autophagy and establishes ErbB2 as a therapeutic target for AD.

Members of the ErbB receptor tyrosine kinase family are highly expressed in the central nervous system of vertebrates, where they are essential for neural development (55□–57). ErbBs form various homodimers and heterodimers to activate downstream signaling pathways upon ligand binding. A recent study showed that activated ErbB1 can inhibit autophagy by mediating tyrosine phosphorylation of Beclin-1 to modulate Vps34 kinase activity. On the contrary, ErbB1 also works as an autophagy initiator by interacting with Rubicon in a kinase-independent manner. Our data revealed that either overexpression or knockdown of EGFR/ErbB1 simultaneously increased the levels of C99 and AICD suggesting that ErbB1 might play dual roles in the regulation of autophagy pending different cellular contexts. In the present study, we provided direct evidence demonstrating that ErbB2 can actively govern the proteostasis of the uncleaved γ-secretase substrate (C99) and the cleaved product (AICD) most likely through modulation of autophagic flux. Our findings suggest that ErbB2 can cause disassembly of the Beclin-1–Vps34–Vps15 complex, and thereby inhibit the initiation of autophagy. Down-regulation of ErbB2 using CL-387,785 or shErbB2 rescues the formation of the Beclin-1–Vps34–Vps15 complex. Reduction of ErbB2 not only decreases C99 and AICD but also concomitantly attenuates Aβ production without significantly affecting the physiological function of γ-secretase (unchanged Notch signaling). Nonetheless, our findings are in line with the current concept that aberrant autophagic flux is key to the proteinopathy-elicited pathogenesis of neurodegenerative diseases. The aberrant expression/activation of ErbB2 may thus predispose toward the development of AD.

Our work also demonstrates that the homeostasis of APP processing and Aβ production can be selectively manipulated without compromising the physiological functions of other γ-secretase substrates, such as Notch. This newly identified function of ErbB2 plays a more prominent role in hindering autophagy initiation than the EGFR/ErbB1 does, because monomeric ErbB2 can effectively disassemble the Beclin-1–Vps34–Vps15 complex. Given that activated EGFR/ErbB1 can bind and phosphorylate Beclin-1 (19), our present study thus suggests a novel molecular basis by which ErbB2 may act as a scaffold of Beclin-1 to keep autophagy activity at a resting state in the absence of EGF signal. These findings thus favor a model in which ErbB2 could work as the gatekeeper of autophagic flux (Fig. S3). In accordance with the increased levels

of ErbB2 in the hippocampus of patients with sporadic AD, it is very likely that the ErbB2-mediated suppression of autophagy chronically contributes to the accumulation of APP-CTFs, leading to the uncontrolled increase in Aβ production and the consequent demise of hippocampal neurons during the pathogenesis of sporadic AD. Our data also suggest that ErbB2 might play a more prominent role than EGFR/ErbB1 does in the progression of AD, because EGFR/ErbB1 expression is not significantly changed in AD brain

Conclusion: we have identified a critical function of oncogenic receptor tyrosine kinase ErbB2 in its monomeric form and provide proof-of-concept evidence suggesting that increased levels of ErbB2 in the hippocampus could potentially be established as a diagnostic marker of sporadic AD. Our data unveil the molecular basis that positions ErbB2 in the driver's seat to maintain autophagy at a resting state. These findings also favor a model in which ErbB2 serves as the negative regulator of autophagy initiation and implicate ErbB2 as an alternative therapeutic target for novel AD therapies.

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