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THE DEVELOPMENT OF *ERBB2*-TARGETED THERAPY FOR ALZHEIMER'S DISEASE

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g-Secretase-catalyzed production of amyloid-b (Ab) underlies the pathogenesis of Alzheimer's disease (AD). To identify genetic modifiers that can selectively affect g-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 g-secretase substrates, APP C-terminal fragment (C99), and extracellular domain truncated notch (NΔE). An RNAi screen examining the effects of lentiviral shRNA clones targeting 777 kinases and 237 phosphatases encoded in the human genome 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 be the most prominent regulatory signaling network that was predicted 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 Ab40, 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 Ab 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 wk significantly improves the cognitive functions of APP/presenilin-1 (PS1) transgenic mice. These findings unveil a noncanonical function of *ErbB2* in modulating autophagy and establishe *ErbB2* as a novel therapeutic target for AD.