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Rab21, a novel PS1 interactor, regulates γ-secretase activity via PS1 subcellular distribution

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The γ-secretase has been a therapeutically target for its key role in cleaving APP to generate β-Amyloid (Aβ), the primary constituents of senile plaques and a hallmark of Alzheimer's Disease (AD) pathology. Recently, γ-secretase associating proteins showed promising role in specifically modulating APP processing while sparing Notch signaling; however, the underlying mechanism is still unclear. A Co-Immunoprecipitation (Co-IP) coupled with mass spectrometry proteomic assay for Presenilin1 (PS1, the catalytic subunit of γ-secretase) was firstly conducted to find more γ-secretase associating proteins. Gene ontology analysis of these results identified Rab21 as a potential PS1 interacting protein, and the interaction between them was validated by reciprocal Co-IP and immunofluorescence assay. Then, molecular and biochemical methods were used to investigate the effect of Rab21 on APP processing. Results showed that overexpression of Rab21 enhanced Aβ generation, while silencing of Rab21 reduced the accumulation of Aβ, which resulted due to change in γ- secretase activity rather than α- or β-secretase. Finally, we demonstrated that Rab21 had no effect on γ-secretase complex synthesis or metabolism but enhanced PS1 endocytosis and translocation to late endosome/lysosome. In conclusion, we identified a novel γ-secretase-associating protein Rab21 and illustrate that Rab21 promotes γ-secretase internalization and translocation to late endosome/lysosome. Moreover, silencing of Rab21 decreases the γ-secretase activity in APP processing thus production of Aβ. All these results open new gateways towards the understanding of γ-secretase-associating proteins in APP processing and make inhibition of Rab21 a promising strategy for AD therapy.

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