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"Interaction of Amyloid Precursor Protein Processing and Valosin-Containing Protein Function"

By

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Cell Biology, Neuroscience and Physiology Program
B.S. China Pharmaceutical University, 2020
M.S. Drexel University, 2021

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Monday, March 16th, 2026
Cancer Center, G1196
10:00 A.M.

Join Zoom presentation

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ABSTRACT

The Amyloid Precursor Protein (APP), a genetic cause of Alzheimer's disease, is a type-I transmembrane protein that is metabolized by proteolysis in the endolysomal system. APP is processed via two pathways: the non-amyloidogenic pathway, where metabolites of α-CTF and p3 are generated; and the amyloidogenic pathway, where metabolites including β-CTF and Aβ peptides are generated. Both full-length APP and its metabolites are secreted by cells in extracellular vesicles (EVs), but the content and function of APP-containing EVs remain unknown. We used genetically humanized rats to isolate App-EVs from primary neuronal conditioned media, followed by electron microscopy to confirm their vesicular identity. Further proteomic analysis identified the Valosin-containing protein (Vcp) as molecular cargo. Vcp helps maintain proteostasis by unfolding ubiquitinated proteins, and it facilitates protein degradation at endolysosomal compartments. Therefore, we probed for Vcp's functional relevance to App-EVs. Pharmacological inhibition of Vcp activity decreased cellular α-CTF levels and caused increased global EV secretion. While Vcp activity modulates the trafficking of App, App mutations independently influence the sorting of its metabolites. The Swedish App mutation (App^S), which promotes amyloidogenic processing, reduced App-EV abundance. While humanized control App-EVs were enriched in full-length App and α-CTF, App β-CTF was undetectable in EVs despite its high cellular levels in App^S, suggesting selective sorting mechanism based on epitopes generated by nonamyloidogenic processing. Indeed, exogenous p3, which contains the α-cleaved neoepitope, induced a dose-dependent increase in small EVs from App^S neuronal cultures, indicating that the α-cleaved neoepitope promotes EV biogenesis. To determine the in vivo consequence of App processing on Vcp function, we crossed *Vcp* mutant rats with *App* lines that either favor amyloidogenic or nonamyloidogenic App processing. We found that amyloidogenic *App* variants were able to induce dystocia when crossed with *Vcp* mutants, whereas non-amyloidogenic *App* variants did not induce this effect. Our findings highlight the importance of Vcp in the regulation of App-EV sorting and secretion and establish Vcp knock-in rats as powerful models that may help bridge Vcp-dependent proteostasis with AD-related pathology.