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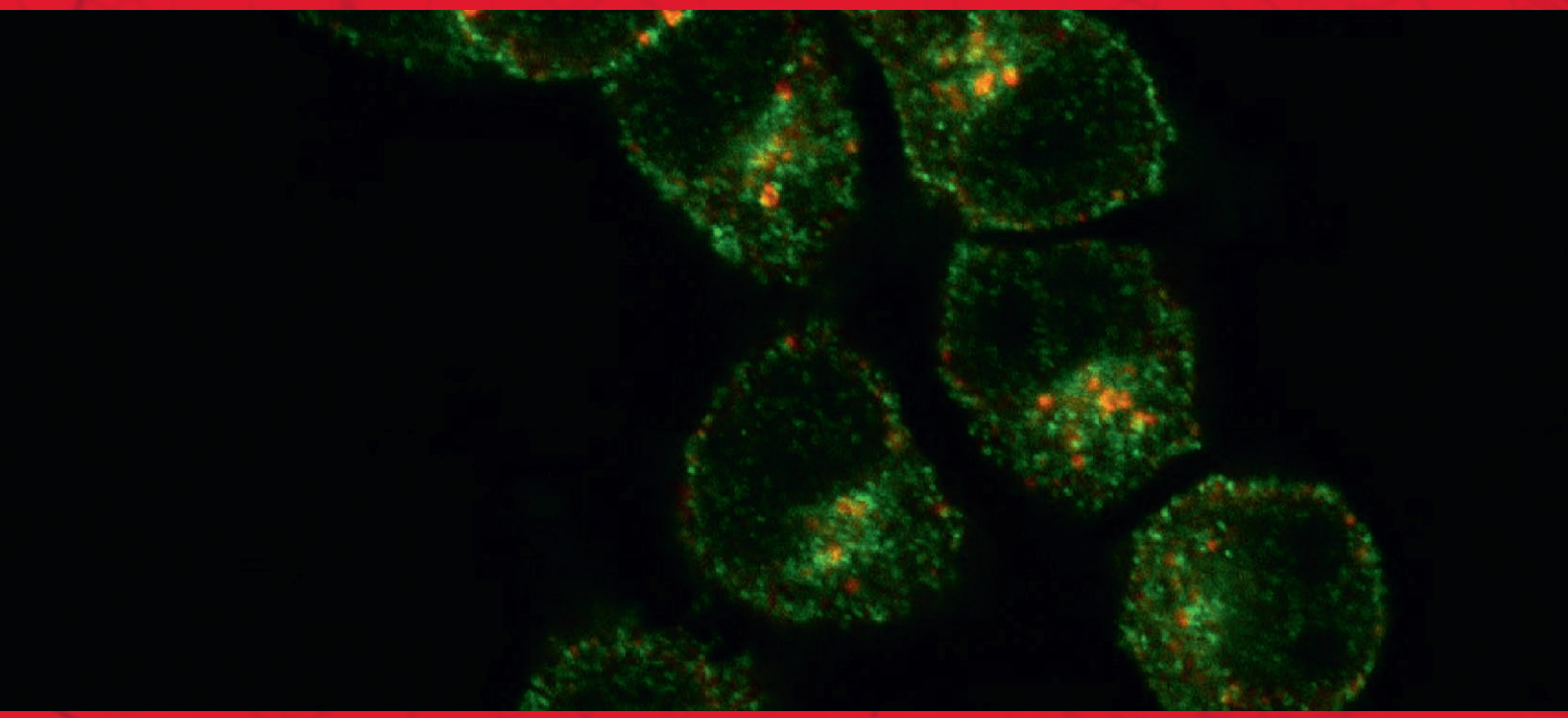

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Front cover: Accumulating evidence suggests that endocytic pathway deficits are involved in Alzheimer's disease pathogenesis. Several reports show that endocytic disturbance affects β-amyloid peptide (Aβ) cleavage from β-amyloid precursor protein (APP). Presenilin-1 (PS1) is the catalytic core of the γ-secretase complex required for Aβ generation. Previously, we showed that aging induces endocytic disturbance, resulting in the accumulation of Aβ and APP in enlarged endosomes. It remains unclear, however, whether PS1 localization and function are affected with endocytic disturbance. Here, we report that in endocytic disturbance PS1 is transported from endosomes to ER/Golgi compartments via retromer trafficking, and that PS1 interacts with VPS35 both in vitro and in vivo. Moreover, PS1 is degraded by proteasomes via a Rab2-dependent trafficking pathway, only during endocytic disturbance. These findings suggest that PS1 levels and localization in endosomes are regulated by retromer trafficking and ER-associated degradation system, even if endocytic disturbance significantly induces the endosomal accumulation of APP and BACE1. Results of this study also suggest that retromer deficiency can affect PS1 localization in endosomes, where Aβ cleavage mainly occurs, possibly leading to enhanced Aβ pathology. The cover image shows that VPS35 knockdown causes endosomal accumulation of PS1 in cells with endocytic disturbance.

Read the full article '*Retromer and Rab2-dependent trafficking mediate PS1 degradation by proteasomes in endocytic disturbance*' by N. Ueda, T. Tomita, K. Yanagisawa and N. Kimura (*J. Neurochem*. 2016, vol. 137 (4), pp. 647–658) on doi: 10.1111/jnc.13586