



SCAMP5 coordinates AP-4-dependent sorting of ATG9A for presynaptic autophagy by recruiting PI4KIII β and generating PtdInsP4 at the trans-Golgi network

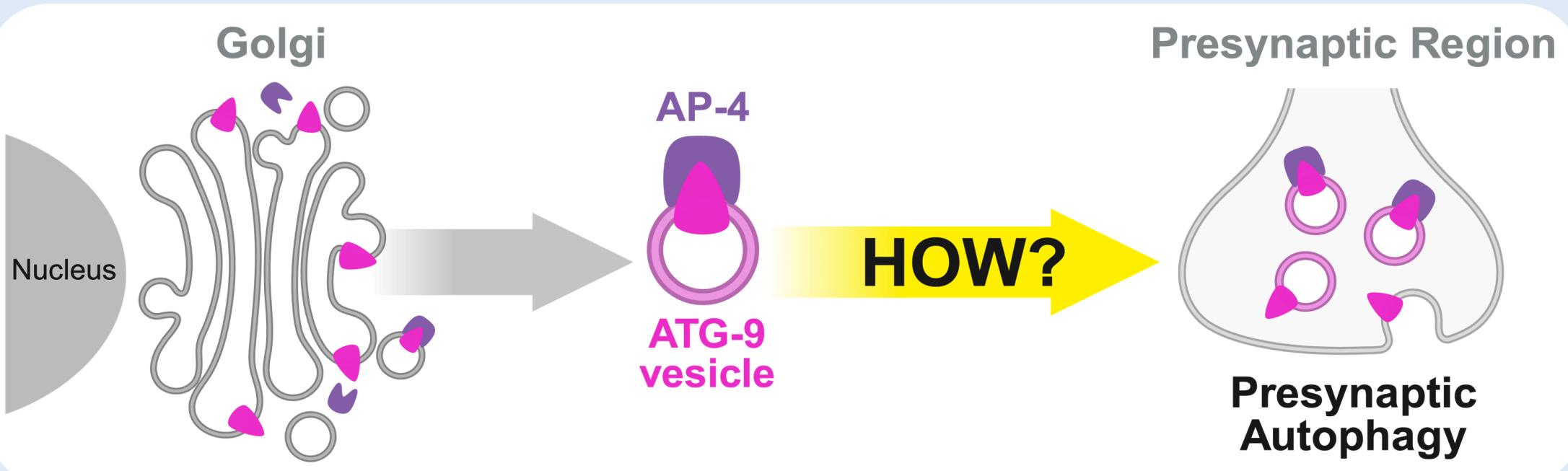
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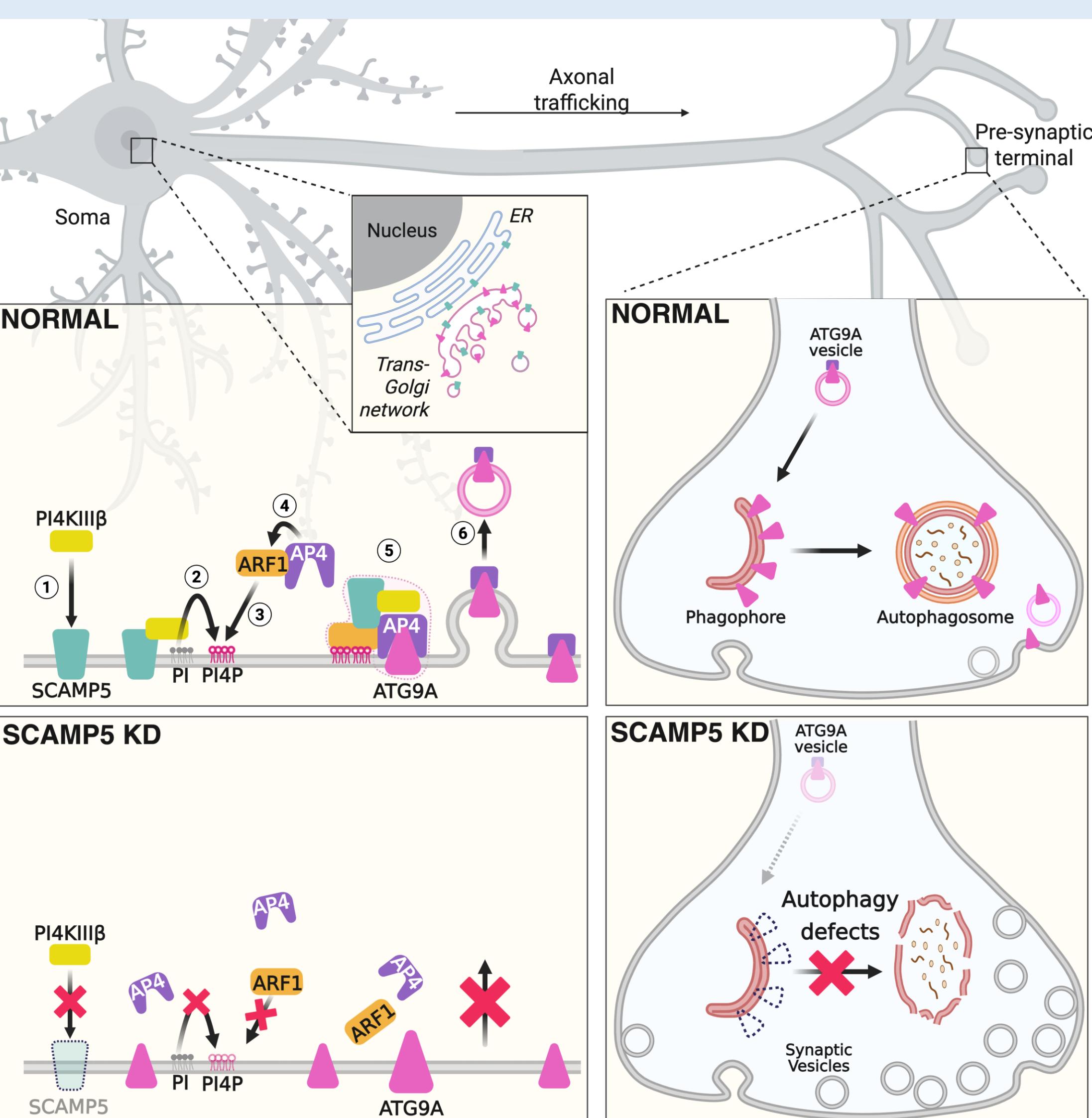
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Abstract



Presynaptic autophagosome formation requires the trafficking of ATG9A, an autophagy transmembrane protein that serves as a specific cargo of the AP-4 complex at the trans-Golgi network (TGN). However, the molecular mechanisms governing ATG9A sorting at the TGN for presynaptic delivery remain poorly understood.



Here, we identify SCAMP5, a synaptic vesicle protein critical for presynaptic plasticity, as highly enriched at the TGN and essential for presynaptic autophagosome formation. SCAMP5 knockdown significantly impaired autophagosome assembly at presynaptic boutons. Mechanistically, we demonstrate that SCAMP5 interacts with phosphatidylinositol 4-kinase III β (PI4KIII β) to regulate its TGN recruitment, thereby controlling local phosphatidylinositol 4-phosphate (PtdIns4P) production. Since PtdIns4P is required for AP-4 recruitment to the TGN, SCAMP5 depletion disrupts this process, leading to abnormal ATG9A accumulation at the TGN and impaired axonal trafficking. Consequently, presynaptic autophagy is compromised, disrupting synaptic protein turnover and homeostasis. These findings establish SCAMP5 as a critical regulator of ATG9A-dependent presynaptic autophagy through its control of PI4KIII β recruitment and PtdIns4P synthesis at the TGN, revealing a novel mechanism linking synaptic vesicle machinery to presynaptic protein quality control.

Fig 1. SCAMP5 knockdown leads to defects in the presynaptic autophagosome formation

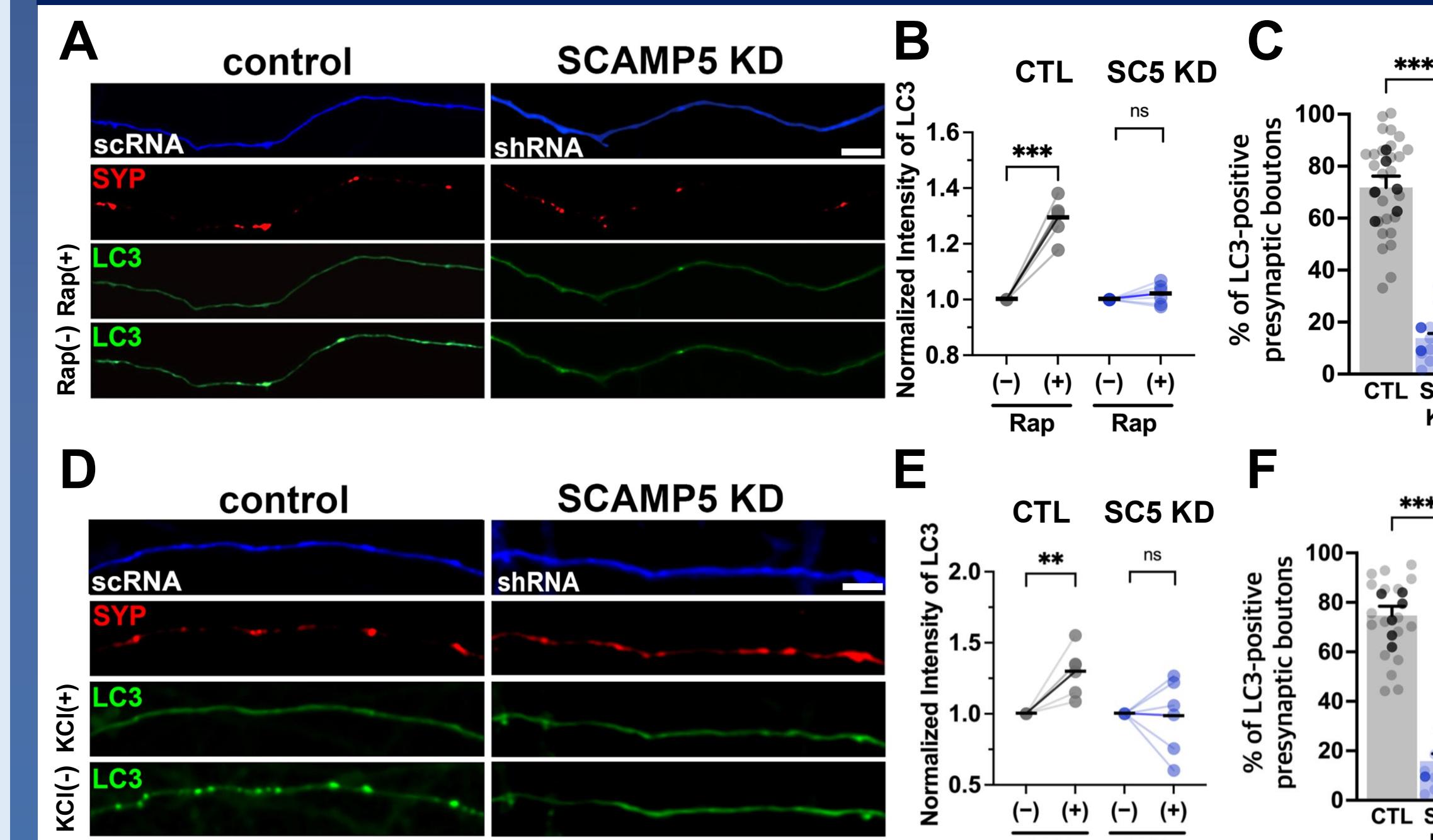


Fig 4. Endogenous ATG9A accumulates in the TGN of both SCAMP5 knockdown and ap4m1 knockout neurons

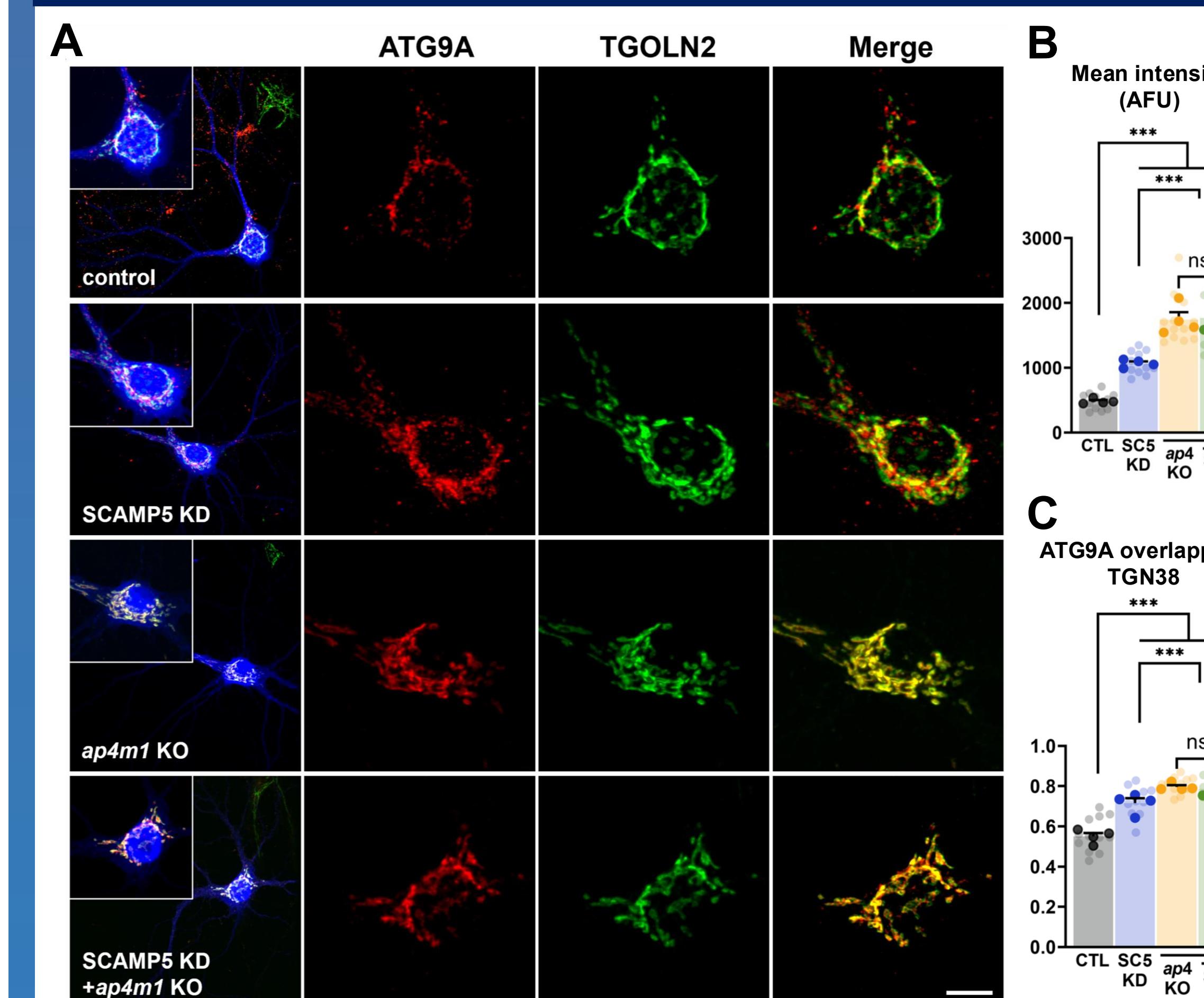


Fig 2. SCAMP5 interacts with PI4KB, which is essential for PI4KB localization and subsequent PtdIns4P production at the TGN

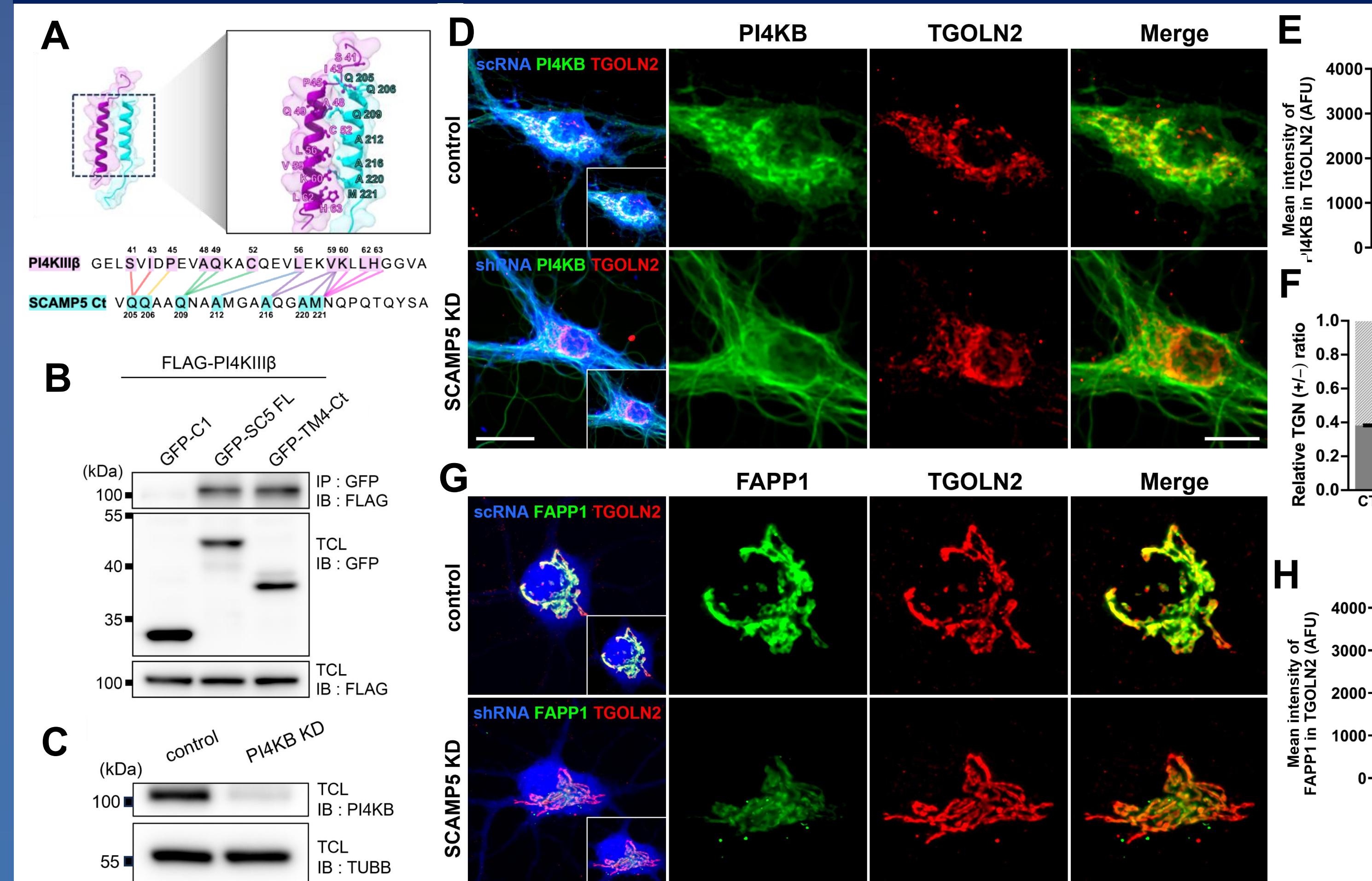


Fig 5. Defects in ATG9A trafficking along the axon to the presynaptic terminals are observed in both SCAMP5 knockdown and ap4m1 knockout neurons

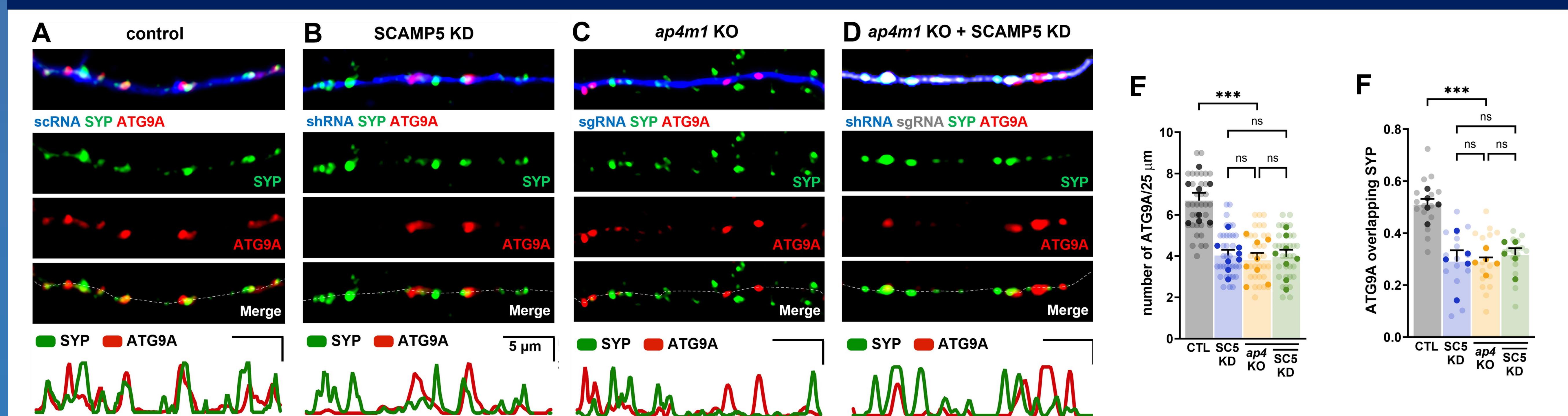
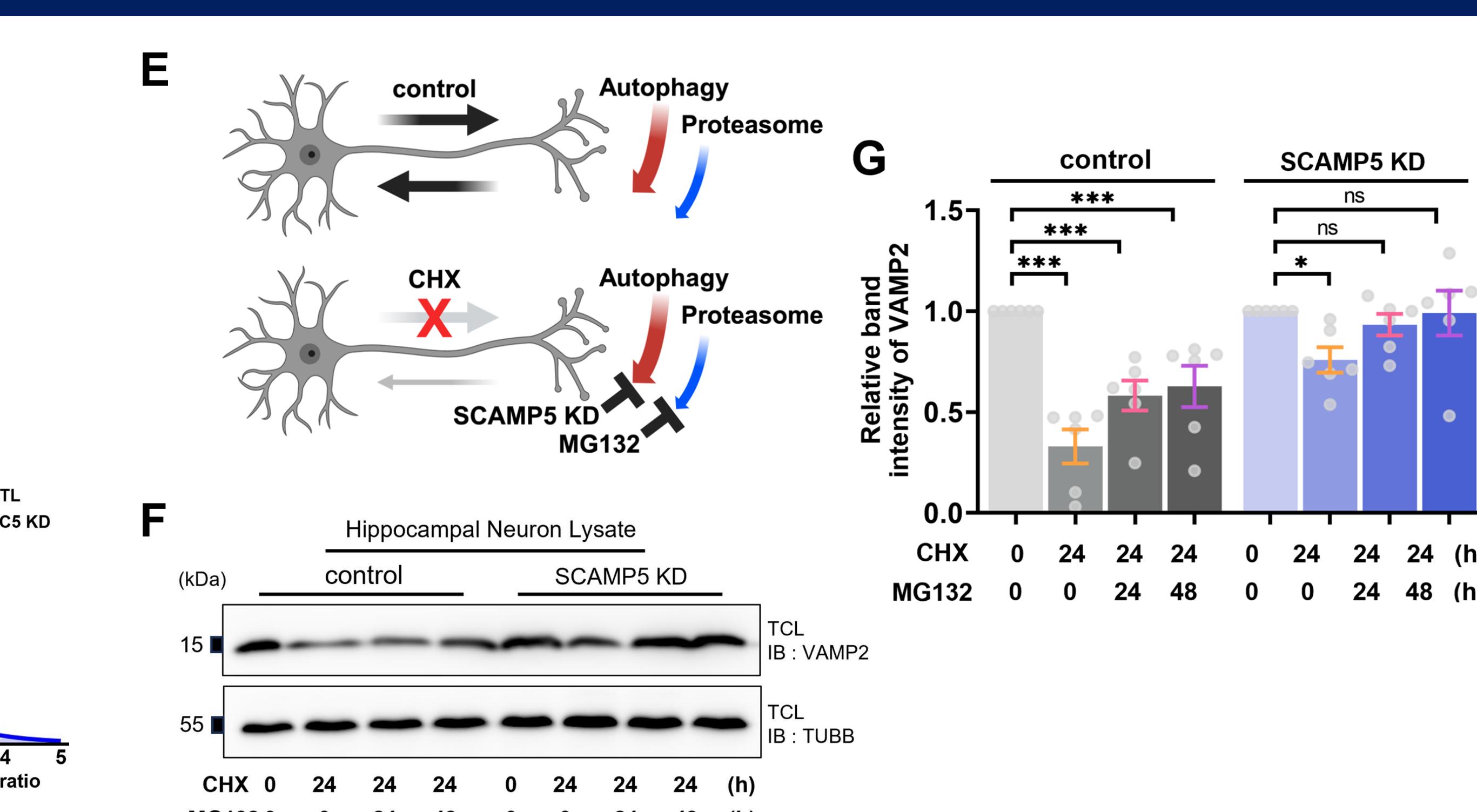
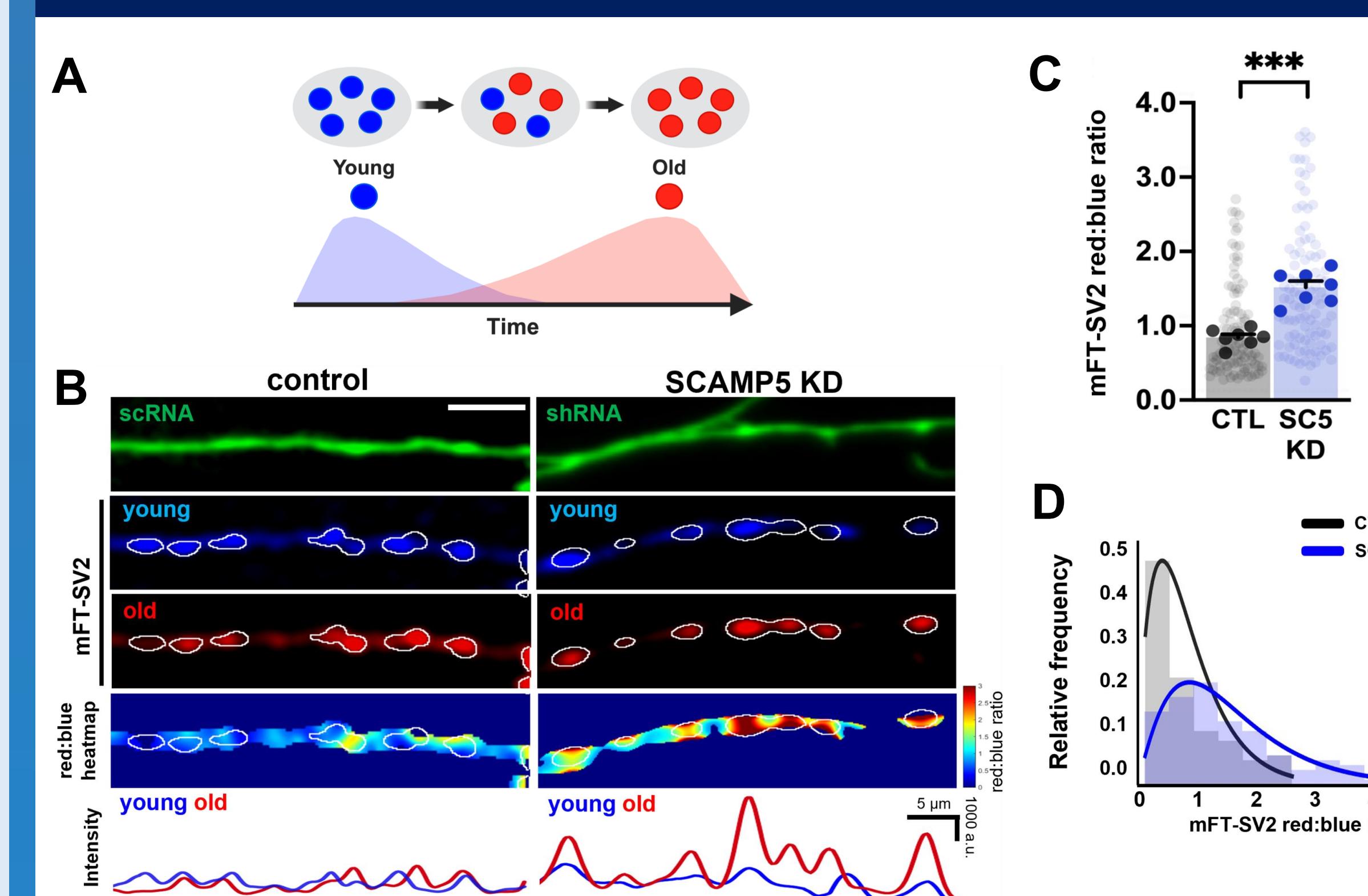


Fig 6. The turnover of presynaptic proteins is impaired with SCAMP5 knockdown



Discussion

This study demonstrates that SCAMP5 at the TGN regulates presynaptic autophagy by modulating PI4KB-dependent PtdIns4P production, which recruits AP-4 and ARF1 to facilitate ATG9A trafficking to presynaptic terminals. SCAMP5 loss impairs axonal ATG9A trafficking and synaptic vesicle protein turnover, revealing SCAMP5 as a molecular nexus integrating vesicle trafficking with protein homeostasis. Given that SCAMP5 mutations and deficiency are linked to autism spectrum disorder, intellectual disability, and epilepsy—conditions sharing autophagy dysfunction—these findings highlight the therapeutic potential of targeting SCAMP5-mediated autophagy in neurodevelopmental disorders.