Multifaceted Function of SCAMP5 in Coordinating Presynaptic Short-Term Plasticity and Autophagy

Sunghoe CHANG

Department of Physiology and Biomedical Sciences, Seoul National University College of Medicine, South Korea

Email: sunghoe@snu.edu

Presynaptic terminals require precise coordination between rapid timescale processes—neurotransmitter release and vesicle recycling—and slower timescale mechanisms of protein quality control through autophagy. The molecular architecture enabling this temporal and spatial integration has remained enigmatic. We reveal that secretory carrier membrane protein 5 (SCAMP5) functions as a central organizing hub that coordinates these seemingly disparate processes through a unified strategy: orchestrating protein-protein interactions at distinct subcellular locations to maintain presynaptic homeostasis across multiple timescales.

SCAMP5 employs its 2/3 loop domain as a versatile interaction interface, binding different partner proteins in spatially segregated compartments to coordinate three interconnected aspects of presynaptic function. At the active zone, SCAMP5-AP2 interaction facilitates release site clearance during intense activity, preventing vesicular protein accumulation that would otherwise cause frequency-dependent short-term depression. This rapid clearance mechanism is essential because it creates spatial availability for subsequent release events. Simultaneously, SCAMP5 regulates the quality of each release event by controlling synaptic vesicle acidification through its interaction with the cation/H+ exchanger NHE6, thereby determining glutamate loading and quantal size. At the trans-Golgi network, SCAMP5 orchestrates a distinct function by recruiting PI4KB to generate PtdIns4P, enabling AP-4-mediated ATG9A trafficking that initiates presynaptic autophagy for long-term protein homeostasis.

These three functions converge to establish SCAMP5 as a master coordinator that links the efficiency of vesicle release (through site clearance), the strength of each synaptic event (through vesicle pH regulation), and the sustainability of synaptic function (through autophagy-mediated protein quality control). Loss of SCAMP5 simultaneously disrupts this integrated regulatory network, causing compounding deficits that manifest as presynaptic dysfunction. As both

SCAMP5 and NHE6 are autism candidate genes, our findings suggest that autism-associated presynaptic dysfunction may arise from disruption of this coordinated regulatory system rather than failure of individual mechanisms, establishing SCAMP5 as a critical integration point where acute synaptic transmission meets long-term presynaptic homeostasis.