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Septin dynamics are essential for exocytosis

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Abstract

Septins are a family of 14 cytoskeletal proteins that dynamically form hetero-oligomers and organize membrane microdomains for protein complexes. The previously reported interactions withSNAREproteins suggested the involvement of septins in exocytosis. However, the contradictory results of up- or down-regulation of septin-5 in various cells and mouse models or septin-4 in mice suggested either an inhibitory or a stimulatory role for these septins in exocytosis. The involvement of the ubiquitously expressed septin-2 or general septin polymerization in exocytosis has not been explored to date. Here, by nano-LC with tandem MS and immunoblot analyses of the sep-tin-2 interactome in mouse brain, we identified not only SNARE proteins but also Munc-18-1 (stabilizes assembled SNARE complexes), N-ethylmaleimid--sensitive factor (NSF) (disassembles SNARE complexes after each membrane fusion event), and the chaperones Hsc70 and synucleins (maintain functional conformation of SNARE proteins after complex disassembly). Importantly, α-soluble NSF attachment protein (SNAP), the adaptor protein that mediates NSF binding to the SNARE complex, did not interact with septin-2, indicating that septins undergo reorganization during each exocytosis cycle. Partial depletion of septin-2 by siRNA or impairment of septin dynamics by forchlorfenuron inhibited constitutive and stimulated exocytosis of secreted and transmembrane proteins in various cell types. Forchlorfenuron impaired the interaction between SNAP-25 and its chaperone Hsc70, decreasing SNAP-25 levels in cultured neuroendocrine cells, and inhibited both spontaneous and stimulated acetylcholine secretion in mouse motor neurons. The results demonstrate a stimulatory role of septin-2 and the dynamic reorganization of septin oligomers in exocytosis.

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