Introduction: alpha-Synuclein is a major component of Lewy bodies (LB) in several neurodegenerative diseases, including Parkinson's disease. Many previous studies focused on the functions of intracellular alpha-synuclein that is abundant in neuronal cytoplasm and extracellular alpha-synuclein, which might accelerate neurotoxicity at each single cell base. It has been reported recently that monomeric and aggregated alpha-synuclein is secreted from neurons by exocytosis. Extracellular alpha-synuclein aggregates have neurotoxic effects, which imply that alpha-synuclein can transmit its neurotoxicity to neighboring cells and tissues.

Aims: To explain the exocytic mechanism of alpha-synuclein, we investigated the possible interactions between alpha-synuclein and rab proteins known to regulate exocytosis.

Methods: With immunoprecipitation and Western blotting, we studied the possible interactions between rab family proteins and alpha-synuclein. cDNA and siRNA transfections were applied to identify the effector molecules and their effects on exocytosis. Inhibition of exocytosis were performed with Exo I and botulinum toxin. With confocal laser scanning microscopy, all these effects were confirmed.

Results: We show that Rab3A and Rab3IP negatively regulate exocytosis of alpha-synuclein through the interactions with alpha-synuclein in SH-SY5Y neuroblastoma cells. The exocytosis can contribute to neuroprotection against alpha-synuclein burden.

Conclusions: These results suggest alpha-synuclein can be exocytosed by the regulation of rab protein family to provide pathological mechanism of Parkinson's disease and other neurodegenerative synucleinopathies.