Function of a gene involved in polarized transport and application to the therapy for human diseases

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Abstract

In polarized cells such as epithelial cells and neurons, newly synthesized proteins are transported to distinct parts of the cell surfaces by polarized transport machinery. Transport vesicles containing proteins fuse with the plasma membrane via the facilitation of SNARE proteins. SNAP23 is one of the SNARE proteins and is involved in exocytotic events in diverse cells. However, the *in vivo* function of SNAP23 remains largely unknown. Recently, we generated some tissue-specific *Snap23* knockout (KO) mice. The loss of SNAP23 in the exocrine and endocrine pancreas resulted in decreased and increased fusion of granules to the plasma membrane, respectively. These results demonstrate opposing roles for SNAP23 in the secretion mechanisms of the endocrine and exocrine pancreas. Furthermore, we identified a low-molecular-weight compound, MF286, which binds specifically to SNAP23 and promotes insulin secretion in mice. Additionally, the central nervous system-specific ablation of SNAP23 results in mice with severe hypoplasia of the neocortex and no cerebellum, suggesting that SNAP23 is necessary for the brain development.

Background & Results

Cell polarity is essential for the generation of our tissues and their physiological functions. In the polarized cells such as epithelial cells and neurons, newly synthesized secretory or membrane proteins are transported to distinct parts (apical and basolateral in epithelial cells or axon and dendrite in neurons) of the cell surfaces by polarized transport machinery. Transport vesicles containing proteins fuse with the plasma membrane via the facilitation of SNARE proteins. In humans, 38 SNARE proteins have been identified. Each SNARE protein exhibits distinct tissue expression and intracellular localization as well as complex formation with its appropriate partners. SNAP23 is one of the SNARE proteins and is involved in exocytotic events in diverse cells. However, the *in vivo* function of SNAP23 in polarized transport remains largely unknown. To know the *in vivo* function of SNAP23, we generated some tissue-specific *Snap23* KO mice. The exocrine-specific KO mice showed decreased fusion of zymogen granules, but the endocrine-specific KO mice showed increased fusion of insulin granules and improved glucose tolerance. These results suggest that SNAP23 plays opposite roles in secretion in the exocrine and endocrine pancreas. Furthermore, we found that the SNAP23-binding compound MF286 promoted insulin secretion and improved glucose tolerance in mice. Additionally, loss of SNAP23 in the central nervous system results in severe hypoplasia of the cerebral cortex and lacked a hippocampus and cerebellum. We found that SNARE complex composed of SNAP23, VAMP8, and Stx1B mediates the localization of N-cadherin to the apical plasma membrane and is crucial for the polarization of neural progenitor cells in the developing brain.

Significance of the research and Future perspective

Our KO studies revealed the different functions of SNAP23 in the pancreas and brain. SNAP23-inhibitor MF286 promotes insulin secretion and improved glucose tolerance in mice, suggesting MF286 may be a candidate drug for diabetes. Furthermore, our findings may have a potential to elucidate the pathogenesis of human brain disorders such as hydrocephalus, spina bifida, and Dandy-Walker syndrome.

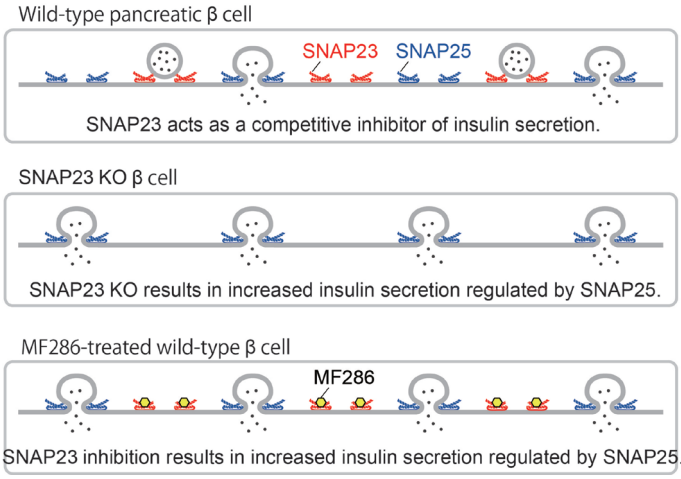

Fig.1 Inhibitory role of SNAP23 for insulin secretion in the pancreatic β cells.

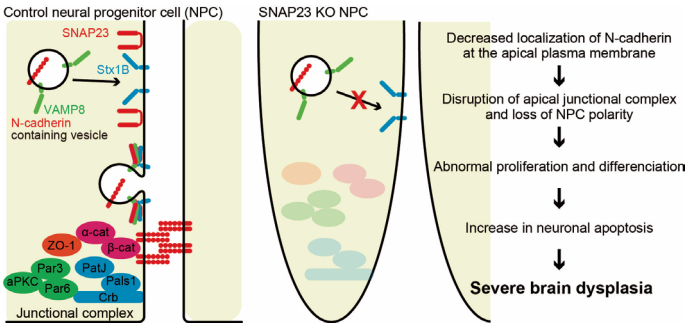

Fig.2. Function of SNAP23 for polarization of the neural progenitor cells.

Patent	Japanese Patent Application No.2017-068871, Japanese Unexamined Patent Publication No.2018-168132
Treatise	Kunii, Masataka; Ohara-Imaizumi, Mica; Takahashi, Noriko et al. Opposing roles for SNAP23 in secretion in exocrine and endocrine pancreatic cells. J Cell Biol. 2016 Oct 10;215(1):121-138. doi: 10.1083/jcb.201604030. Kunii, Masataka; Noguchi, Yuria; Yoshimura, Shin-ichiro et al. SNAP23 deficiency causes severe brain dysplasia through the loss of radial glial cell polarity. J Cell Biol. 2021 Jan 4;220(1):e201910080. doi: 10.1083/jcb.201910080.
URL	https://www.harada-lab.online/
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