News Release

Title

Identification of a new mechanism for selective endocytosis

Key points

1. Endocytosis of various types of nutrients and membrane proteins is essential for cellular survival, homeostasis, migration, and other processes. The mechanisms that regulate the selectivity and specificity for endocytosis, however, have not completely been revealed.

2. The present study showed that a protein complex composed of Girdin and dynamin GTPase regulates selective endocytosis.

3. The study might lead to the understanding of mechanisms for some human diseases including neural diseases and cancers.

Summary

Eukaryotic cells have a function to uptake various nutrients and membrane proteins, depending on the types of cells and their contexts, which is termed “endocytosis”. For the distinct functions of cells, the specificity and selectivity for the nutrients and membrane proteins (also termed “cargoes”) and their timing and spacing must be precisely controlled.

The present study, reported by Professor Masahide Takahashi, Associate Professor

Atsushi Enomoto and Designated Assistant Professor Weng Liang in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), identified a novel mechanism for selective endocytosis. The research group revealed that Girdin, which they have been interested in for long time, is a binding protein for dynamin GTPase that is a key regulator for the scission of membrane vesicles from the plasma membrane. They found that the differential interaction of Girdin with some cargoes, which competitively prevent Girdin from interacting with dynamin, confers the cargo selectively for endocytosis. Therefore, Girdin regulates transferrin and E-cadherin endocytosis but has no effect on integrin and epidermal growth factor (EGF) receptor endocytosis.

Previous studies have shown the significance of Girdin in the neural development, tumorigenesis of some cancers, and angiogenesis. Therefore, the researchers expect that the present study leads to the identification of mechanisms for the development of some human diseases and cancer progression. The study was published online in *The EMBO Journal* in July, 24, 2014.

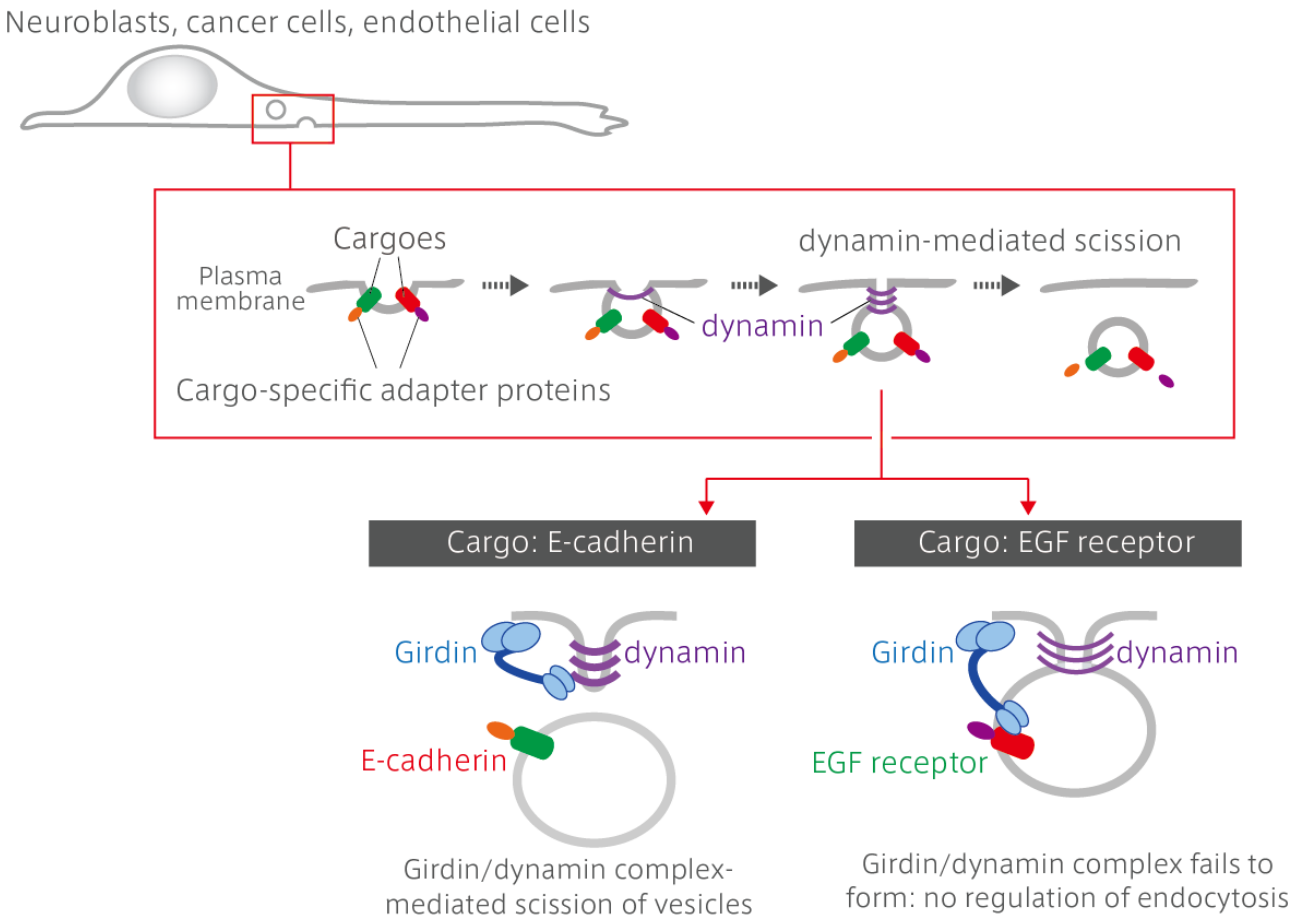
Research background

Eukaryotic cells have a function to uptake various nutrients and membrane proteins, depending on the types of cells and their physiological and pathological contexts, which is termed "endocytosis". For the distinct functions of cells, the specificity and selectivity

for the nutrients and membrane proteins (cargoes) and their timing and spacing must be precisely controlled. It has been demonstrated that cargo-specific adaptors (such as AP-2 protein complex, Numb, beta-arrestin, epsin, etc.) are determinants for the selective endocytosis (see Figure). However, given the limited number of known adaptor proteins and the variety of cargoes that are selectively internalized, additional mechanism(s) that govern selective endocytosis remain to be identified.

Research results

In the process of endocytosis, the plasma membrane undergoes remodeling to form membrane vesicles, which are then pinched off by the activity of dynamin GTPase, a key regulator for the scission of membrane vesicles. The research group revealed that Girdin, which is an actin-binding protein that they have been interested in for long time, is a new binding protein for dynamin. They found that the differential interaction of Girdin with some cargoes, which competitively prevent Girdin from interacting with dynamin and confers the cargo selectively for endocytosis (see Figure). Therefore, Girdin regulates transferrin and E-cadherin endocytosis but has no effect on integrin and epidermal growth factor (EGF) receptor endocytosis. The results revealed that Girdin regulates selective endocytosis via a mechanism involving dynamin, but not by operating as a cargo-specific adaptor.



Research summary and future perspective

The study has identified a new mechanism for selective endocytosis, which helps us understand how cells differentially control the endocytosis of distinct cargoes. Previous studies reported by the same group and others have shown the significance of Girdin in neural development, adult neurogenesis in the hippocampus, the progression of breast cancers and brain tumors, and postnatal angiogenesis. Therefore, the researchers expect that the present study leads to the identification of mechanisms for some human diseases.

The authors and title of the paper

Liang Weng, Atsushi Enomoto, Hiroshi Miyoshi, Kiyofumi Takahashi, Naoya Asai, Nobuhiro Morone, Ping Jiang, Jian An, Takuya Kato, Keisuke Kuroda, Takashi Watanabe, Masato Asai, Maki Ishida-Takagishi, Yoshiki Murakumo, Hideki Nakashima, Kozo Kaibuchi, Masahide Takahashi. Regulation of cargo-selective endocytosis by dynamin 2 GTPase-activating protein girdin. The EMBO Journal, July 24, 2014.

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http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2014/girdin_20140724jp.pdf