News Release

Title

Negative regulation of amino acid signaling by MAPK-regulated 4F2hc/Girdin complex

Key Points

1. We identified endocytosis-related protein Girdin forms a complex with amino acids transporter 4F2 heavy chain (4F2hc) in a mitogen-activated protein kinase- and amino acid signaling-dependent manners.
2. Girdin induces 4F2hc endocytosis, which subsequently leads to the decreased cell surface 4F2hc and lowered cytoplasmic glutamine and leucine content.
3. Girdin negatively regulates amino acids-induced mTORC1 activation via interaction with 4F2hc.

Summary

The mechanistic target of rapamycin complex 1 (mTORC1) protein kinase is a master regulator of cell growth, which senses several extracellular signals, such as growth factors and nutrient levels, to coordinate cell metabolism. The activation of mTORC1 by amino acids requires many proteins such as Rag GTPase, GATOR and Ragulator. However, how cells negatively regulate amino acid signaling remains largely unknown. In the present study reported by Professor Masahide Takahashi, Asscociate Professor Atsushi Enomoto and Designated Assistant Professor Liang Weng in Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.), we revealed that an endocytosis-related protein Girdin negatively regulates amino acids-induced mTORC1 activation via forming a complex with 4F2 heavy chain (4F2hc), a subunit of multiple amino acid transporters. Girdin/4h2hc complex formation, which requires growth factor-induced Girdin phosphorylation and amino acids-induced 4F2hc ubiquitination, promotes the internalization of 4F2hc to the lysosome. The resultant decrease in cell surface 4F2hc leads to lowered cytoplasmic glutamine and leucine content, which then downregulates amino acids-induced mTORC1 activation. These findings uncovered the mechanism underlying negative regulation of mTORC1 signaling, which may play a role in tightly regulated cell growth and metabolism. Previous studies have shown the significance of mTORC1

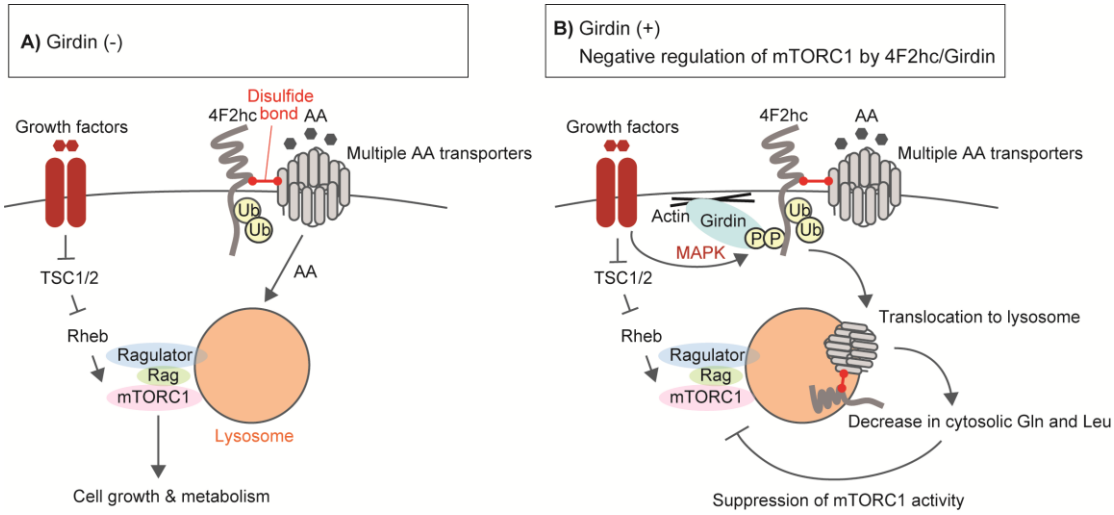
signaling pathway is involved in a variety of physiological and pathological processes, such as the development of diabetes, cancer, and neurodegenerative disease. Therefore, the researchers expect that the present study will extend our understanding on the mechanism for the development of these diseases. This study was published online in *PLoS Biology* on March 14, 2018.

Research background

Cell signaling pathways need to be precisely controlled so that cells can respond appropriately to the external cues and maintain cell homeostasis. The mTORC1 pathway integrates amino acid and growth factor signaling by distinct mechanisms in which several small guanosine triphosphatases (GTPases) play important roles. For example, growth factor stimulation activates mTORC1 via the GTPase Rheb, whereas amino acids activate mTORC1 through the heterodimeric Rag, adenosine diphosphate ribosylation factor-1 (Arf1), and Rab1 GTPases. Among these, Rag GTPases, which are tightly regulated by the guanine nucleotide exchange factor (GEF) Ragulator and the GTPase-activating protein (GAP) GATOR downstream of amino acid sensors including Castor, sestrin 2 and SAMTOR, are the most studied. Although the mechanisms by which cells transmit amino acid signaling to mTORC1 have been elucidated, it remains largely unknown how cells negatively regulate amino acid signaling.

Research results

Amino acids transporter 4F2hc was previously reported to regulate mTORC1 activation. We have been interested in the biological function of Girdin for a long time, and identified Girdin as an actin-binding and endocytosis-related protein. In the present study, we further revealed that 4F2hc interacts with Girdin in mitogen-activated protein kinase- and amino acid signaling-dependent manners to translocate to the lysosome. The resultant decrease in cell surface 4F2hc leads to lowered cytoplasmic glutamine and leucine content, which downregulates amino acid signaling. Consistently, Girdin depletion augments amino acid-induced mTORC1 activation and inhibits amino acid deprivation-induced autophagy (See Figure). These findings uncovered the mechanism underlying negative regulation of amino acid signaling, which may play a role in tightly regulated cell growth and metabolism.



Research summary and future perspective

These findings uncovered the mechanism underlying negative regulation of mTORC1 signaling, which helps us to understand how cell growth and metabolism are elaborately regulated. We also have shown that Girdin is essential for the development of postnatal brain and adult neurogenesis, the progression of breast cancers and brain tumors, where it may have a role in maintaining appropriate activation of mTORC1. Therefore, we expect that the present study will lead to the discovery of underlying mechanisms for related human diseases.

Publication

Weng L, Han YP, Enomoto A,Kitaura Y, Nagamori S, Kanai Y, Asai N, An J, Takagishi M, Asai M, Mii S, Masuko T, Shimomura Y, Takahashi M. Negative regulation of amino acid signaling by MAPK-regulated 4F2hc/Girdin complex. *PLoS Biology*, March 14, 2018.

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