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Review

Rab27a in pancreatic beta-cells, a busy protein in membrane trafficking

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ABSTRACT

The small GTPases have the 'active' GTP-bound and 'inactive' GDP-bound states, and thereby act as a molecular switch in cells. Rab27a is a member of this family and exists in T-lymphocytes, melanocytes and pancreatic beta-cells. Rab27a regulates secretion of cytolytic granules from cytotoxic T-lymphocytes and intracellular transport of melanosomes in melanocytes. In pancreatic beta-cells, Rab27a controls pre-exocytotic stages of insulin secretion. A few GTP-dependent Rab27a effectors are known to mediate these cellular functions. We recently found that Rab27a also possesses the GDP-dependent effector coronin 3. Coronin 3 regulates endocytosis in pancreatic beta-cells through its interaction with GDP-Rab27a. These results imply that GTP- and GDP-Rab27a actively regulate distinct stages in the insulin secretory pathway. In this review, we provide an overview of the roles of both GTP- and GDP-Rab27a in pancreatic beta-cells.

Contents

1. Introduction

Diabetes mellitus is defined as chronic hyperglycemia due to relative insulin deficiency. Impairment of the secretory activity in pancreatic beta-cells is seriously involved in the pathogenesis of this disease. In particular, decreased output in the early phase of glucose-induced insulin release precedes the onset of type 2 diabetes mellitus (Ashcroft and Rorsman, 2004; Kahn, 2001). Insulin secretion is composed of several sequential stages: insulin synthesis and its packaging into secretory granules, granule transport in the cytoplasm, granule interaction with the cell membrane, and exocytosis as a result of an increase in cytoplasmic Ca^{2+}. The present study reviews a recent progress in the understanding of the roles of the small GTPase Rab27a and its effectors in the secretory pathway.

2. The Rab cycle

There are two types of GTP-binding proteins (G proteins): heterotrimeric G proteins and small GTPases. Both G proteins regulate various cellular functions (Takai et al., 2001; Wennerberg et al., 2005). The small GTPases are monomeric and their molecular weights range 20–30 kDa. Ras proteins are oncogene products that are the founder molecules identified as small GTPases. Today, based on the difference in structure, sequence and function, the small GTPases are divided into the Ras, Rho, Rab, Arf and Ran subfamilies.

The Rab family, consisting of more than 60 members, regulates membrane traffic in its specific cells. The intracellular localization of Rab proteins is determined by their specific regulators, therefore some Rab proteins can be used as organelle markers. They interconvert GTP- and GDP-bound forms, and their binding to GTP or GDP causes conformational changes. The GTP-bound form interacts with its effectors and transmits a specific signal downstream. In contrast, the GDP-bound form has been regarded as an

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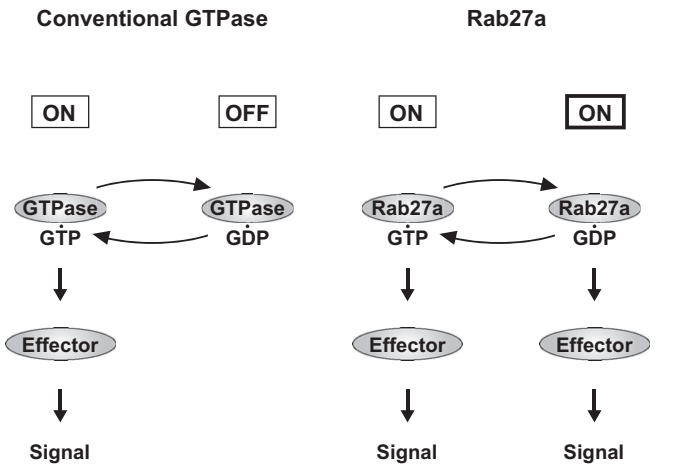

Fig. 1. Atypical regulation by Rab27a via its GDP-bound form. The GTPase has the GTP- and GDP-bound states. Conventionally, the GDP-bound GTPase is regarded as inactive, because any functional effectors of this state have not been identified (left). However, we have recently found that Rab27a has a GDP-dependent effector, which enables us to challenge the traditional dogma (right).

inactive form, because the functional binding partner of this form has not been identified (Fig. 1). Recently, we searched for novel Rab27a-interacting proteins in pancreatic beta-cells and identified coronin 3 (Kimura et al., 2008). Unexpectedly, coronin 3 is functionally active when it binds GDP-Rab27a. Thus, we concluded that coronin 3 is a genuine GDP-dependent Rab27a effector. Rab27a also possesses the typical GTP-dependent effectors. Therefore, these results indicate that Rab27a is not a simple on-off switch but a regulator that controls distinct functions through its GTP- and GDP-dependent effectors (Fig. 1).

Several molecules regulate the GTP/GDP exchange and intracellular localization of the small GTPases (Fig. 2). Typically, the small GTPases bind GDP via their interaction with GDP dissociation inhibitors (GDIs) (Dirac-Svejstrup et al., 1994; Garrett et al., 1994; Ullrich et al., 1994). GTP/GDP exchange proteins (GEFs) promote the GTP/GDP exchange reaction and render the GTPases active (Novick and Zerial, 1997). GTPase activating proteins (GAPs) activate the intrinsic GTPase activity and exchange the small GTPases to the GDP-bound form (Fukui et al., 1997). Each small GTPase has its specific GDI, GEF and GAP. These proteins regulate the function and localization of the relevant GTPase.

3. Roles of Rab27a and its effectors

Rab27a is a member of the Rab family that is involved in the control of membrane traffic (Zerial and McBride, 2001). Rab27a is the first Rab protein to be closely associated with human diseases. Mutations in the Rab27a gene cause a human genetic disease, Gricelli syndrome. Patients suffering from Gricelli syndrome exhibit immunodeficiency and pigment dilution in hair (Menasche et al., 2000; Pastural et al., 2000). Identification and the characterization of its effectors revealed the roles of Rab27a in Rab27a-expressing cells such as T-lymphocytes and melanocytes. Rab27a regulates secretion of cytolytic granules from cytotoxic T-lymphocytes and intracellular transport of melanosomes in melanocytes (Bahadoran et al., 2001; Haddad et al., 2001; Hume et al., 2001; Kuroda and Fukuda, 2004; Menasche et al., 2000; Stinchcombe et al., 2001; Wilson et al., 2000). The Rab27a effectors first identified are members of the synaptotagmin-like protein (Slp) family. The Slp family, comprising five distinct Slp isoforms (Slp1-5), contains an N-terminal Slp homology domain (SHD) and two C-terminal tandem domains called C2A and C2B (Fukuda, 2005). SHD consists of two regions (SHD1 and SHD2). SHD1 is the GTP-Rab27a binding site, and SHD2 is required for high affinity of GTP-Rab27a binding and stability of the SHD structure (Fukuda, 2002, 2003). Slp homologue lacking C2 domains (Slac2) family also possesses SHD domains. Slac2c (also called as MyRIP) acts as a linker between GTP-Rab27a and the motor proteins MyoVa or MyoVIIa, and transports melanosomes along actin filaments (Fukuda and Kuroda, 2002). However, Noc2 and Munc13-4, putative Rab27a effectors, do not contain SHD, suggesting that they may bind GTP-Rab27a in a different fashion from the Slp and Slac2 families.

In pancreatic beta-cells, Rab27a is abundantly expressed and localized on the certain spots of dense core granules (Yi et al., 2002). Ashen mice with natural-occurring mutation in Rab27a show glucose intolerance with decreased insulin secretion (Kasai et al., 2005). Therefore, Rab27a has been proposed to regulate insulin secretion. To investigate relevant molecular mechanisms, identification of Rab27a effectors in pancreatic beta-cells were attempted vigorously. Eventually, Slac2c/MyRIP, Noc2 and Slp4/granuphilin were found (Izumi et al., 2003). It should be noted that all these effectors are GTP-dependent (Fig. 3).

Slac2c/MyRIP possesses different functions in pancreatic beta-cells from those in melanocytes. MyoVa is also present in pancreatic beta-cells and participates in insulin granule movement (Ivarsson et al., 2005; Varadi et al., 2005). Although Slac2c/MyRIP is involved in the transport of insulin granules on actin filaments, the interaction of Slac2c/MyRIP and MyoVa in insulin granule transport has not been detected in one report (Waselle et al., 2003). Therefore, it is possible that Slac2c/MyRIP may regulate insulin secretion via a distinct mechanism.

Noc2 possesses 78% similarity to the N-terminus of rabphilin-3A, a Rab3a effector abundant in brains (Kotake et al., 1997).

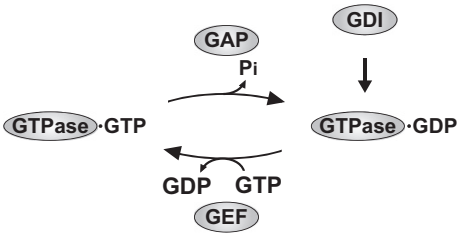

Fig. 2. Regulatory mechanisms of a small GTPase. Exchange of a small GTPase between the GTP- and GDP-bound forms is controlled by GDI, GEF and GAP. Typically, the small GTPase binds GDP via its interaction with GDI. GEF promotes the GTP/GDP exchange reaction and renders the GTPase active. GAP activates the intrinsic GTPase activity and changes the small GTPase to the GDP-bound form.

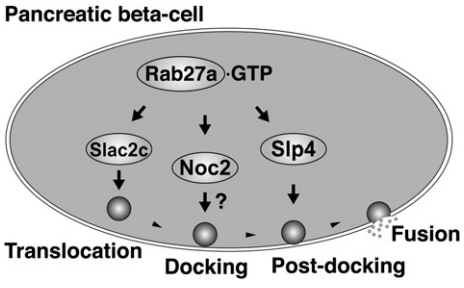

Fig. 3. GTP-dependent Rab27a effectors in pancreatic beta-cells. Slac2c/MyRIP, Noc2 and Slp4/granuphilin are Rab27a effectors in pancreatic beta-cells. Slac2c/MyRIP is involved in the transport of insulin granules on actin filaments. Noc2 regulates insulin secretion by modulating actin dynamics. Slp4/granuphilin binds syntaxin1a and docks insulin granules to the inner surface of cell membrane. It should be noted that all these effectors are GTP-dependent.