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Review

Rab GTPases implicated in inherited and acquired disorders

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ABSTRACT

The endocytotic machinery imports, transports and exports receptors and associated molecules between the plasma membrane and various cytoplasmic chambers resulting in selective recycling, degradation, or secretion of molecules and signaling complexes. Trafficking of receptors, growth factors, nutrients, cytokines, integrins as well as pathogens dictates the kinetics and magnitude of signal transduction cascades. Understandably, alterations in the 'fate' of such cargo complexes have profound physiologic and pathophysiologic implications. Rab GTPases regulate endocytosis by decorating intracellular vesicles and targeting these vesicles along with their cargoes to appropriate subcellular compartments. In the last decade, the number of genetic diseases driven by germline mutations in Rab GTPases or their interacting proteins [1–3], has increased and there is growing evidence of aberrant Rab GTPase function in acquired pathophysiologies such as immune deficiency, infection, obesity, diabetes and cancer.

Contents

Abbreviations: ER, endoplasmic reticulum; EEA, early endosome antigen; GDP, guanosine diphosphate; GDI, GDP dissociation inhibitor; GEF, guanine exchange factor; GAP, GTPase activating protein; GLUT4, glucose transporter 4; GTP, guanosine triphosphate; MAPK, mitogen activated protein kinase; PI3K, phosphoinositide-3 kinase; PM, plasma membrane; RAB, Ras in the brain; REP, Rab escort protein; RCP, Rab coupling protein; RTK, receptor tyrosine kinase; SNARE, soluble NSF attachment receptors; SHH, Sonic Hedgehog; TGN, trans-Golgi network.

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1. Introduction

1.1. Targeting vesicular trafficking

A dynamic endomembrane system compartmentalizes the eukaryotic cell into chemically (pH) and functionally distinct subcellular domains. This is crucial for maintaining protein stability, cell polarity, motility, differentiation and signal transduction [2,4–6]. Rab GTPases along with SNARES are the key player in regulating vesicular trafficking. Yet, we are only beginning to comprehend the far-reaching consequences of aberrant endocytosis in health and disease. A number of comprehensive reviews summarizing the molecular, physiological and pathological aspects of vesicular trafficking are available which underscores the importance of this infrastructure within the cell [2,5,7,8]. From a clinical aspect, the most critical question is what is the role of aberrant vesicular trafficking and abnormal Rab GTPase function in inherited and acquired diseases and as an important corollary, the question arises how can we target the "master organizers" of vesicular trafficking and improve patient outcomes?

In an effort to provide insights into this question, we have highlighted systems where disruption of vesicular trafficking, arising from aberrations in Rab proteins, their regulators, as well as Rab effectors, contribute to monogenic inherited disorders or multigenic conditions such as diabetes or cancer and update the reader on recent advances in the field [9].

1.2. Structure and function of Rab GTPases

Ubiquitously expressed in eukaryotes, Rab/Ypt/Sec4 GTPases constitute the largest subgroup of Ras small GTPases [10]. Originally described as Ras-like proteins in brain (Rab), there are 11 Rab proteins in yeast, an organism with a relatively simple endomembrane system. In contrast, the number of Rab proteins steadily increased along evolution to about 70 putative family members in humans, paralleling an increase in the complexity of vesicular trafficking system [1,11].

According to the seminal work of Pereira-Leal and Seabra, five diagnostic sequences identify a bona fide Rab GTPases amidst other similar GTPases [10]. For in depth discussion regarding the structure of Rabs, reviews of Pfeiffer's et al., should be visited [12–14], however, it suffices to state that the GTP binding sites and variable C-terminals impart the necessary specificity to act as molecular switches controlling downstream effector interactions.

With only 30% average sequence homology, Rab proteins are a diverse group of small GTPases associated with vesicular trafficking functions, including ensuring transport specificity and demarcating organelle identity. Although some Rabs appear to have generalized housekeeping functions others have tissue or cell type specific roles (Fig. 1). A significant number of Rab proteins appear to have redundant functions and for many family members, function remains unknown [15]. Additionally, Rab proteins and their effectors couple endomembrane to motor proteins and the cytoskeleton [16] facilitating transport of these vesicles and their cargoes to appropriate compartments. Thus, in a multistep process, Rab proteins facilitate vesicle formation via budding from the donor compartment, transport to the acceptor compartment, vesicle fusion and release of the vesicle content into the appropriate acceptor compartment [17–21]. From a cell signaling standpoint, Rab proteins provide spatiotemporal regulation of signaling which impacts amongst others processes, cell polarity, growth, as well as migration [6,22].

1.3. Activation and membrane cycles of Rab GTPases

Commonly, Rab proteins undergo a membrane association and dissociation cycle, partially in tandem with the GDP/GTP cycle, to allow exchange of cargo between specific membrane domains (Fig. 1). GDP/GTP cycling is controlled by two interrelated pro-

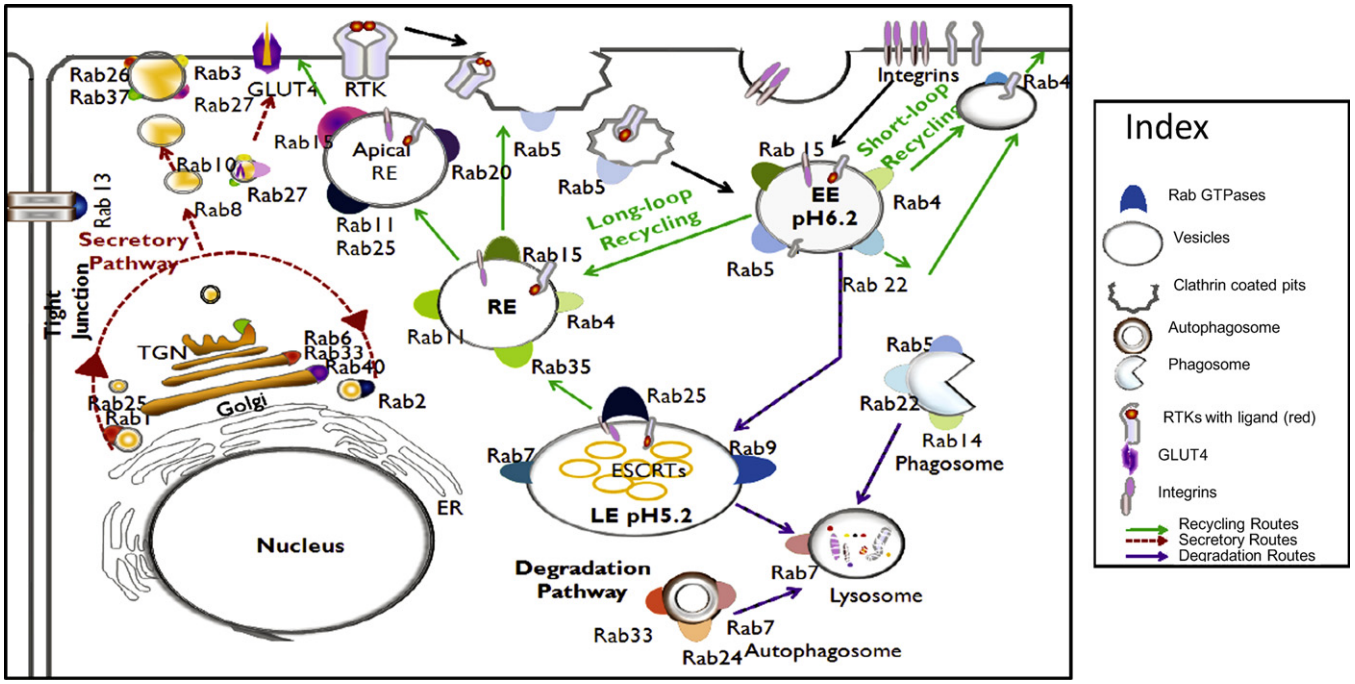

Fig. 1. RabGTPases mediated vesicular trafficking: Rab GTpases are involved in trafficking of cell membrane receptors including RTKs, GLUT4 and integrins. Rab5 facilitates fusion of clathrin-coated vesicles containing activated receptor to EE. The cargo is then sorted either to Rab4 decorated vesicles for fast-track recycling or to Rab11 decorated long loop slow recyling endosomes. Alternatively, for attenuation of signal transduction, the cargo laden vesicles are targetted to the lysosome via Rab7 and Rab9 coated late endosomes. The endosomal sorting complex (ESCRT) recognizes ubiquitinated proteins and routes them for degradation. Rab GTPases such as Rab3, Rab10 and Rab27 play critical role in the exocytosis/secretory pathway, while Rab1 and 2 are necessary for ER–Golgi transport. Receptor ligand complexes are differentially sensitive to pH, a fact that is utilized by the vesicular trafficking machinery to uncouple the signalosome.