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Review

Signal transduction gRABs attention

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Abstract

Rab proteins are small GTPases involved in the regulation of vesicular membrane traffic. Research done in the past years has demonstrated that some of these proteins are under the control of signal transduction pathways. Still, several recent papers point out to a new unexpected role for this family of Ras-related proteins, as potential regulators of intracellular signaling pathways. In particular, several evidence indicate that members of the Rab family of small GTPases, through their effectors, are key molecules participating to the regulation of numerous signal transduction pathways profoundly influencing cell proliferation, cell nutrition, innate immune response, fragmentation of compartments during mitosis and apoptosis. Even more surprisingly, direct involvement of Rab proteins in signaling to the nucleus has been demonstrated. This review will focus on aspects of Rab proteins function connected to signal transduction and, in particular, connections between membrane traffic and other cell pathways will be examined.

Keywords: Rab proteins; Small GTPases; Signal transduction; Signaling pathways; Phosphorylation; Kinases

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1. Introduction

Membrane traffic has been extensively studied in the past years and huge amount of data are now available on how transport of lipids, protein and particulate matter is regulated. In particular, it is becoming clear how cargo is selected in the appropriate vesicle and how vesicles recognize and fuse with the appropriate compartment [1–3].

The Rab family of small GTPases is heavily involved in the regulation of vesicular transport [4,5]. Indeed, Rab GTPases are key regulatory molecules that control mem-

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brane trafficking events in eukaryotic cells. Human cells contain more than 60 Rab proteins that are localized to distinct vesicular compartments and regulate specific steps of membrane transport. Rab proteins recruit on membrane one or more effector proteins that mediate formation of transport vesicles, tethering and docking of vesicles, motor protein-dependent movement therefore facilitating ultimate fusion between membrane compartments (see [6–8] for review).

Recently, several studies have demonstrated a close connection between membrane traffic and signal transduction [9–11]. Signal transduction pathways direct a variety of cellular processes, including gene expression (through the action of more than 2000 transcription factors encoded by the human genome), cell survival, cell growth, differentiation, proliferation, cell cycle, apoptosis and several other fundamental cellular events [12].

Lately, a close connection between Rab proteins function and signal transduction pathways has been revealed. In this review we will focus on aspects of signaling pathways that involve, directly or indirectly, Rab proteins.

2. Phosphoinositide kinases

All eukaryotic cells, from yeast to mammals, contain phoshoinositides, which are formed from phosphorylation of the head group of phosphatidylinositol (PtdIns). The enzymes responsible for these reactions are termed phosphoinositide kinases and, through the formation of phoshoinositides, they control cellular processes as important as proliferation, survival, cytoskeletal organization, vesicle trafficking, glucose transport and platelet function. Phosphoinositide kinases are usually divided in three families: phosphoinositide 3-kinase (PI3K), PtdIns 4-kinases (PtdIns4Ks) and PtdIns-P (PIP) kinases (PIP5Ks) [13]. The localization of these kinases and of the corresponding PtdIns phosphatases leads to the precise distribution of the individual PtdIns species in different subcellular compartments. Proteins containing PtdIns-binding motifs, among which the FYVE, PhoX homology, pleckstrin homology, ENTH and ANTH domains, ultimately localize to the corresponding membrane domains where they exert their different functions.

Among the different families, PI3Ks have been particularly well studied for their initial involvement in the control of cellular growth and apoptosis and, more recently, in key steps of membrane trafficking. It is therefore not surprising a cross-talk between Rab GTPases and members of the PI3K family of proteins. Indeed, Rab5 appears to be important for the recruitment of hVPS34/p150, a class III PI3K, to the early endosomes, through its GTP-dependent interaction with p150 [14]. Consequently, PtdIns(3)P, a privileged product of hVPS34/p150, is found at high levels in the membrane of these structures [15,16], recruiting FYVE and PhoX domain-containing proteins such as the Rab5 effectors EE1A, Rabenosyn-5, Rabip4′ and the kinesin KIN16B [17–20] which participate both in the basic vesicle formation process and in the intracellular movement of these organelles. More recently, also Rab7 has been identified as as an important regulator of late endosomal hVPS34 function [21], suggesting this kinase as a key player of vesicle maturation between early and late endosomes.

Rab5 has represented the first example of a protein of the Rab family directly interacting with a class I PI3K, p85α/p110β [22], consisting of a catalytic p110 isoform associated with a regulatory subunit, p85α. As this PI3K is profoundly involved in signaling controlling cellular growth and survival, its interaction with Rab5 may suggest a role for this Rab GTPase also in these processes. Indeed, several observations already support this suggestion. Not only Rab5 interacts with p85α/p110β but also leads to efficient coupling of the lipid kinase product to one of its most important downstream targets for what concerns cell survival, Akt [23]. Similarly, Rab4, a Rab protein involved in insulin action, controls PI3K and Akt activation [24]. Last, recent studies implicated Rab25 in aggressiveness of epithelial cancers, possibly through the activation of the PI3K/Akt pathway [25]. Indeed, high-density array comparative genomic hybridization (CGH) showed amplification of an area of chromosome 1q22 where Rab25 is localized, in approximately half of ovarian and breast cancers. Increased levels of the GTPase were also associated with decreased survival in these types of cancers [25]. As concerns the mechanism mediating Rab25 effects on tumor aggressiveness, the inhibition of apoptosis was associated with a decrease in expression of the proapoptotic molecules, BAK and BAX, and activation of the antiapoptotic PI3K and Akt pathway [25]. In line with a potential involvement of Rab proteins in the control of cell proliferation and survival, forced expression of Rab25 also markedly increased anchorage-dependent and anchorage-independent cell proliferation, prevented apoptosis and anoikis, including that induced by chemotherapy, and increased aggressiveness of cancer cells in vivo [25].

The identification of the physical and functional link between Rab proteins and PI3Ks has nonetheless revealed an extraordinary complexity of the reciprocal regulation of these proteins on one another. Based on current knowledge, it is in fact possible to consider these proteins as inserted in an auto-regulatory loop in which, once activated by tyrosine kinase receptor such as the one for EGF [26], Rab5 stimulate PI3K, whose p85 regulatory subunit acts as a GAP on Rab4 and Rab5 itself, therefore regulating how long these GTPases remain in their GTP-bound active state [27]. It is important to note however that these effects may depend on the specific receptor and system used as, for example, in rat adipocytes, insulin stimulates the guanine-nucleotide exchange activity of Rab4, via a PI3K-dependent signaling pathway [28].

The prototype PtdIns4Ks were first cloned from yeast and designated PIK1 [29] and STT4 [30]. Subsequently, cDNAs for two mammalian PtdIns4Ks were cloned and termed PI4Kα and PI4Kβ. The latter is present in the cytoplasm where it is concentrated in the Golgi complex