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EDITORIAL

Rab GTPases, master controllers of eukaryotic trafficking

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Membrane trafficking between cell organelles by vesiculo-tubular carriers is crucial to the existence of eukaryotic cells. Fundamental in ensuring that cargoes are delivered to their correct destinations are the Rab GTPases, a large family of small GTPases that control membrane identity, vesicle transport including coat recruitment, uncoating, fission, motility, target selection and fusion through the recruitment of effector proteins (including sorting adaptors, tethering factors, protein kinases and phosphatases, and motors). Each organelle of both the endocytic and exocytic pathways expresses several Rab proteins, which must be sequentially activated to allow precise delivery, docking and fusion of different membrane compartments. Crosstalk between multiple Rab proteins through shared effectors, or through effectors that recruit selective Rab activators, ensures the spatiotemporal regulation of vesicle traffic. Functional impairments of Rab pathways are associated with diseases, such as immunodeficiencies, cancer and neurological disorders, and many intracellular pathogens have evolved specific mechanisms to modulate or hijack Rab GTPases dynamics and trafficking functions. The present issue of Small GTPases summarizes the main aspects of the state of the art on the various fields where Rab proteins are implicated.

1. Characteristics of the Rab GTPase family

Following Rab activation by structurally unrelated guanine-nucleotide exchange factors (GEFs), each Rab binds a specific set of effector proteins that mediate the various downstream functions of that Rab. Then, with the help of GTPase-activating proteins (GAPs) that enhance the intrinsic GTPase activity, the Rab hydrolyses GTP to GDP, terminating its function. Guanine-nucleotide-dissociation inhibitors (GDIs) recognize GDP-bearing Rabs and can extract them from membranes and redeliver those Rabs to the appropriate target membrane. Matthias P. Müller and Roger S. Goody [1] provide an overview of Rab proteins with a focus on the current understanding of their **regulation by GEFs, GAPs and GDIs**.

Rab GTPases are intrinsically soluble and require a post-translational modification, the addition of geranylgeranyl hydrophobic molecules for membrane association. Rabs first associate with a Rab escort protein (REP) and form a stable complex that is the substrate for the subsequent dual prenylation of C-terminal cysteine motifs via Rab geranylgeranyl transferase (RabGGT). After geranylgeranylation, REP remains bound to Rab and escorts it to the respective target donor membrane. Swapnil R. Shinde and Subbareddy Maddika [2] explain how extensive **post-translational modifications of Rabs** regulate protein–protein interactions, protect them from proteolytic degradation and, most importantly, facilitate membrane attachment and determine their subcellular localization and function.

To catalyze a wide range of very different processes, each Rab interact, in its active form, with a large number of effector proteins and, on the other hand, Rab effectors can interact with multiple, closely related Rabs in different tissues. **Rab partner proteins** include tethering complexes, fusion regulators, motor linkers, sorting adaptors, protein kinases and phosphatases, components of membrane contact sites as well as Rab regulators. Olena Pylypenko, Hussein Hammich, I-Mei Yu and Anne Houdusse [3] explain how these interactions orchestrate the tightly controlled Rab-specific functionalities such as membrane composition, modifications, recruitment of molecular motors for intracellular trafficking, or recruitment of scaffold proteins that mediate interactions with downstream partners, as well as actin cytoskeleton regulation.

2. Cellular functions of Rab GTPases

Autophagy is the evolutionarily conserved degradation pathway and recycling pathway of cellular components that involves the formation of a membrane double layer,

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cargo sequestration, sealing, maturation, and eventual fusion with vacuoles and lysosomes. A number of Rab GTPases, which regulate secretory and endocytic membrane traffic, have been shown to play either critical or accessory roles in autophagy. Rab1, Rab5, Rab7, Rab9A, Rab11, Rab23, Rab32 and Rab33B participate in autophagosome formation whereas Rab9 is required in non-canonical autophagy. Rab7, Rab8B, and Rab24 have a key role in autophagosome maturation. Rab8A and Rab25 are also involved in autophagy but their role is still unknown. Päivi Ylä-Anttila and Eeva-Liisa Eskelinen [4] summarize the **current knowledge on the roles of Rab24 in autophagy and diseases**.

The Golgi complex, central organelle in the secretory pathway, mediates the modification, sorting and transport of proteins and lipids. In mammalian cells, it is structured in the form of a continuous membranous system composed of stacks connected by tubular bridges (the "Golgi ribbon"). Although it adopts an apparently stable organization at the steady state, it is a highly dynamic organelle, and a continuous membrane trafficking, monitored by Rab proteins, is essential to maintain Golgi homeostasis and functions. Of the about70 human Rab proteins, approximately 20 have indeed been associated with the Golgi apparatus. Bruno Goud, Shijie Liu and Brian Storrie [5] overview the available studies concerning Golgi Rabs and highlight how they **act as major determinants of the Golgi complex structure.**

Motile and non-motile (primary) cilia, morphologically distinct plasma membrane-associated projections supported by microtubules, are organelles ancestrally present in many eukaryotic cells. Cilia govern cellular functions ranging from motility to integration of mechanical and chemical signaling from the environment, and are also sites of intense vesicular traffic. Defects in cilia lead to ciliopathies, characterized by a pleiotropic phenotype affecting many tissues and organs. A number of Rab and Rab-like proteins have been functionally associated with the cilium, serving a wide range of roles related to basal body maturation, ciliary axoneme extension, ciliary protein and membrane transport, and cilium-based developmental signaling. Oliver E. Blacque, Noemie Scheidel and Stefanie Kuhns [6] discuss these emerging functions of **Rab proteins in cilium formation, function and diseases**.

Cells release into the extracellular environment diverse types of membrane nanoscale vesicles of endosomal and plasma membrane origin called exosomes. Containing certain combinations of lipids, adhesion and intercellular signaling molecules as well as RNAs, exosomes participate in intercellular communication processes since they can enter the circulation and pass through additional biological barriers. These key mediators may then allow the transfer of genetic and biochemical information between distant cells. Rabs play important roles in both vesicle budding and mobility through interaction with the cytoskeleton. Lionel Blanc and Michel Vidal [7] present the recent advances in our understanding of the **exosome secretion and its regulation by small GTPases of the Rab family**.

Cytokinesis is the terminal stage of eukaryotic **cell division** in which the cytoplasm of a dividing cell is partitioned between two daughter cells. This complex cellular process is marked by the formation of the midbody, a transient organelle that establishes the site of abscission between nascent daughter cells. It requires dramatic remodeling of the cytoskeleton and membrane trafficking pathways, but also of internal vesicular organelles such as the Golgi apparatus. Rabs, well-established regulators of membrane transport, are known to mediate several membrane transport steps including vesicle formation, molecular motor-dependent vesicle transport and targeting of transport vesicles and organelles to their correct destinations. Paulius Gibieža and Rytis Prekeris [8] discuss latest findings about the function of Rabs and polarized membrane transport during different steps of cytokinesis as well as during the final stage of cell division known as abscission.

Cell polarity refers to the asymmetric organization of several cellular components, including cell plasma membrane, cytoskeleton or organelles. It allows cells to carry out their specialized functions, be they epithelial barrier function, transmission of action potentials in nerve cells, or modulation of the immune response. Both the establishment and the maintenance of cell polarity require the directed trafficking of membrane proteins and lipids, essential processes that are led by Rab GTPases. The latter act through an assortment of effector proteins that include scaffolding proteins, cytoskeletal motors as well as other small GTPases. Christopher Cox, Sara S. Parker and Jean M. Wilson [9] highlight the similarities and differences in **Rab function for the instruction of polarity** in diverse cell types.

G protein-coupled receptors (GPCRs) are a superfamily of cell-surface receptors that regulate a variety of cell functions by responding to a myriad of ligands. The magnitude of the response elicited by a ligand depends on the level of receptor available at the plasma membrane. So their physiological functions are dictated by their intracellular trafficking and precise targeting to the functional destinations, then by their removal from the cell surface. Rabs, involved in almost every step of vesicle-mediated transport, contribute to ensure proper surface expression and distribution of GPCRs. Guansong Wang, Zhe Wei and Guangyu Wu [10] examine **the role of Rab GTPases in GPCR cell surface transport**,

particularly post-Golgi traffic, and discuss the underlying molecular mechanisms.

Regulation of ion and solute transport across the membrane of cells and organelles, crucial to many of life's processes, depends on the balance between the function of each channel or transporter and on the number of molecules present. This number of channels present results from an intricate network of proteins that controls the late events of channel trafficking, such as endocytosis, recycling and targeting to lysosomal degradation. Given their fundamental role in specifying identity and routing of vesicles and organelles, Rab proteins are key factors in vesicular trafficking. Carlos M. Farinha and Paulo Matos [11] review the **role of Rab GTPases in regulating trafficking of ion channels and transporters**, comparing what is known for cystic fibrosis transmembrane conductance regulator (CFTR) and epithelial sodium channel (ENaC) with other types of channels.

The development of the mammalian cerebral cortex is a multiphasic process characterized by sequential steps of neural progenitor proliferation, cell cycle exit, neuroblast migration and neuronal differentiation. The cortex development is largely dependent on the neuronal migration from the ventricular zone to the superficial layer of the cortical plate. Rab proteins control multiple steps of neuronal migration. Moreover, neurons have specialized demands on membrane trafficking during both development (wiring-specific extensive arborizations) and function (neurotransmitter release). Maria Lidia Mignogna and Patrizia D'Adamo [12] summarize the known roles of Rabs involved in the maintenance of neuronal vesicular trafficking in the central nervous system in its both aspects, the axonal pre-synaptic trafficking and the dendritic post-synaptic trafficking. A correct orchestration of vesicle movement is indeed essential to maintain neuronal polarity and then to permit an accurate architecture and functionality of **synaptic activity**.

3. Rab proteins and pathologies

Membrane trafficking between organelles by vesiculotubular carriers is fundamental to the existence of eukaryotic cells. Central in ensuring that cargoes are correctly delivered to their destinations are the Rabs. Crosstalk between multiple Rabs through shared effectors, or through effectors that recruit selective Rab activators, ensures the spatiotemporal regulation of the membrane trafficking. Functional impairments of Rab pathways are associated with both genetic (as immunodeficiencies) and acquired (cancers and neurodegenerative disorders) human diseases. Studies on **diseases associated with Rabs** or Rab-interacting proteins have shed light on the important role of intracellular membrane trafficking in disease etiology. Marcellus J. Banworth and Guangpu Li [13] cover recent advances in the field with an emphasis on cellular mechanisms.

Intracellular bacterial pathogens have evolved highly specialized mechanisms to enter and survive within their eukaryotic hosts, where they need to evade detection by the host immune system and to obtain nutrients and biosynthetic precursors. In order to do this, bacterial pathogens create an intracellular niche that is favorable for replication, where they have adopted sophisticated strategies to control intracellular membrane trafficking. Since Rab GTPases are critical regulators of endocytic and secretory membrane trafficking events, many **intracellular pathogens have evolved specific mechanisms to modulate or hijack Rab GTPases** dynamics and trafficking functions. Stefania Spanò and Jorge E. Galán [146] describe the unique trafficking subversion strategies used by three intracellular bacterial pathogens, *Mycobacterium tuberculosis, Salmonella enterica and Legionella pneumophila*.

Viruses are obligate intracellular parasites that must usurp the host cell machinery for many stages of the viral life cycle in order to produce a new generation of infectious virions. In one of the less understood steps of enveloped virus assembly, viral components including the transmembrane glycoproteins, structural proteins and the viral genome have to be targeted to the site of viral budding, where they assemble and are incorporated into a newly formed virion that gains a lipid envelope from a cellular membrane. Rabs appear to be implicated in the replication of many important viral pathogens infecting humans. Paul Spearman [15] provides a summary of **virus-Rab protein interactions**, with a particular focus on the role of Rab-related trafficking pathways on late events in the lifecycle of herpes viruses and of HIV-1.

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