Small GTPases Minireview Series*

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Small GTPases are monomeric guanine nucleotide-binding proteins of 20–25 kDa molecular mass. They play major roles in the regulation of growth, morphogenesis, cell motility, axonal guidance, cytokinesis, and trafficking through the Golgi, nucleus, and endosomes. The first small GTPase to be discovered was Ras, and there are now many members of the Ras superfamily of GTPases. These are grouped in five subfamilies (Ras, Rho, ADP-ribosylation factors (ARF), Rab, and Ran), and each subfamily is featured in this minireview series. When GDP is bound, the GTPases are inactive, and activation occurs when GDP is released and GTP is bound. This exchange is accomplished by proteins called either guanine nucleotide exchange factors (GEFs) or GDP dissociation stimulators (GDSs). The active GTP-bound GTPases interact with a variety of effector proteins to produce their cellular effects. Their activity is time-limited by their intrinsic GTPase activity which is stimulated by GTPase-activating proteins (GAPs). GDP dissociation inhibitors (GDIs) have also been identified for some GTPases, e.g. Rho and ARF.

In the first minireview of the series, Anne B. Vojeck and Chan-ning J. Der discuss cell signaling through Ras. This GTPase is important because it is a key regulator of cell growth and is found in mutated oncogenic forms in a large number of human tumors. When specific residues in Ras are mutated it becomes constitutively active (insensitive to GAP action) and causes cell transformation. The first signaling pathway involving Ras to be discovered was the Raf/MEK/ERK cascade of protein kinases that leads to the stimulation of certain transcription factors. In their review, Vojeck and Der point to additional Ras effectors that have been identified and point out that other pathways besides Raf/MEK/ERK contribute to malignant transformation. These other Ras effectors include p120GAP, which associates with p190RhoGAP, RabGDS, which targets Ral and other proteins, RIN1, which enhances the transforming ability of Bcr/Abl, and phosphatidylinositol (PI) 3-kinase, which generates PI(3,4,5)P₃, an activator of the protein kinases Akt/PKB and PDK1. All these proteins have demonstrated or potential roles in the control of cell growth, morphology, and apoptosis.

The second minireview of the series by Deborah J. G. Mackay and Alan Hall examines the Rho subfamily of GTPases. These proteins come in three major subtypes, namely Rho, Rac, and Cdc42, which control the actin cytoskeleton in distinct ways. The authors discuss the role of certain proteins as effectors of Rho GTPases in the reorganization of the cytoskeleton. One of these is p160Rho kinase, which alters myosin light chain phosphorylation, thus regulating myosin filament assembly and F-actin bundling. Another is the enzyme (PI-4P 5-kinase) that synthesizes the regulatory lipid PI(4,5)P₂. This lipid affects many proteins including the ezrin/radixin/moesin (ERM) family of proteins, which are essential for Rho- and Rac-mediated actin changes. Another major role for the Rho proteins is the regulation of gene transcription, and Mackay and Hall discuss the various pathways (JNK and p38 mitogen-activated protein kinase) and the transcription factors (serum response factor, NFκB) involved. Finally, they consider the astonishingly large number of GEFs for Rho proteins and point out the lack of information on their specific roles and regulation.

The third minireview of the series by Joel Moss and Martha Vaughan explores the ARF subfamily. The first of these was discovered as a factor required for the ADP-ribosylation of the α-subunit of the heterotrimeric G protein G, by cholera toxin. Subsequently it was found that ARFs comprised three classes and were critical components of several vesicular trafficking pathways. In the minireview, the domain structures of the various GEFs for ARFs (ARNO, cytohesin 1, and cytohesin 3) are analyzed in detail. All contain a domain present in Sec7, a yeast gene involved in protein secretion. This domain encodes the GEF activity, and the proteins also contain pleckstrin homology and other domains that bind PI(3,4,5)P₃ and are responsible for membrane binding. The crystal structure of the ARNO Sec7 domain is described in terms of the residues required for ARF binding, and the sites on ARF1 involved in ARNO binding are also analyzed. The properties of ARF GTPases are also discussed in terms of their activation and membrane recruitment by lipids (diacylglycerol, PI(3,4,5)P₃) and receptors for KDEL proteins. In an afterward, the authors point to the relative lack of information about the class II and III ARFs and the molecules that operate and regulate vesicular trafficking.

The fourth minireview of the series by Frauke Schimmoller, Iris Simon, and Suzanne R. Pfeffer describes the Rab GTPases, which number at least 30. These play key roles in the secretory and endocytic pathways and are located in distinct cellular compartments. Rab facilitates the formation of v-SNARE:t-SNARE complexes, which are integral components of vesicle trafficking. It is proposed that Rab acts by recruiting specific docking factors (Exo-cyst, Rabaptins) from the cytosol to facilitate pairing of the SNAREs. In line with other small GTPases, Rab proteins are active in the GTP form, and several Rab-binding proteins (Rabphilin, Rabaptin 5) keep them in this form and thus influence vesicle fusion. Pfeffer and associates also consider the evidence that Rab proteins are required for transport vesicles to form. Finally, they note some key issues that need to be addressed, including the problem of specificity, i.e. how Rab facilitates vesicle targeting to the appropriate membranes and how they induce the formation of correct SNARE pairs.

The last minireview of the series is by Mary Shannon Moore and focuses on Ran, a GTPase that plays a central role in protein and RNA trafficking in and out of the nucleus. It is one of the most abundant GTPases, and cells contain either one or a few isoforms. Macromolecules travel in and out of the nucleus through nuclear pore complexes (NPCs) and utilize different receptors and carriers. However, almost all the receptors that interact with GTP-Ran and are regulated by the Ran GTPase cycle. One GEF for Ran is RCC1 (regulator of chromosomal condensation), which is strategically placed inside the nucleus. A Ran GAP is also described. Interestingly this protein is post-translationally modified by a ubiquitin-like addition, which targets it appropriately to the cytoplasmic entrance to the NPC. The NPC is a very complicated structure with many proteins still uncharacterized. Important are the repeat-containing nucleoporins, which form “tracks” by which transport substrates pass through the NPC. Ran functions to trigger the assembly or disassembly of transport complexes, and an important factor is probably the difference in the concentration of GTP Ran between the nucleus and cytoplasm, but there are many complexities to the process that are examined in the minireview.

* These minireviews will be reprinted in the 1998 Minireview Compendium, which will be available in December, 1998.