

GTP Binding Proteins (Low Molecule Weight)

Key References

- Bernards, A. and Settleman, J., GAP control: regulating the regulators of small GTPases., *Trends Cell Biol.*, **14**, 377-385 (2004).
- Burrige, K. and Wennerberg, K., Rho and Rac take center stage., *Cell*, **116**, 167-179 (2004).
- Colicelli, J., Human RAS superfamily proteins and related GTPases., *Sci STKE*, **2004**, RE13. (2004).
- Etienne-Manneville, S. and Hall, A., Rho GTPases in cell biology., *Nature*, **420**, 629-635 (2002).
- Hall, A., (Ed.) GTPases, *Oxford University Press* (2000).
- Nie, Z., et al., Arf and its many interactors., *Curr. Opin. Cell Biol.*, **15**, 396-404 (2003).
- Pfeffer, S. and Aivazian, D., Targeting Rab GTPases to distinct membrane compartments., *Nature Rev. Mol. Cell Biol.*, **5**, 886-896 (2004).
- Reuther, G.W. and Der, C.J., The Ras branch of small GTPases: Ras family members don't fall far from the tree., *Curr. Opin. Cell Biol.*, **12**, 157-165 (2000).
- Quimby, B.B. and Dasso, M., The small GTPase Ran: interpreting the signs., *Curr. Opin. Cell Biol.*, **15**, 338-344 (2003).
- Spang, A., ARF1 regulatory factors and COPI vesicle formation., *Curr. Opin. Cell Biol.*, **14**, 423-427 (2002).
- Takai, Y., et al., Small GTP-binding proteins., *Physiol. Rev.*, **81**, 153-208 (2001).
- Zerial, M. and McBride, H., Rab proteins as membrane organizers., *Nature Rev. Mol. Cell Biol.*, **2**, 107-117 (2001).

Overview

The approximately 150 members of the human Ras superfamily of low molecular weight GTP binding proteins function as regulators of diverse cellular processes. Most Ras superfamily members have intrinsic GTP hydrolyzing activity, which allows them to cycle between inactive GDP-bound and active GTP-bound states. In their active conformation, Ras family members can interact with a variety of effector proteins. By changing the localization of effectors, by altering their interaction with other proteins, or by modifying their enzymatic activity, Ras superfamily members mediate their diverse downstream functions.

GDP/GTP cycling of Ras superfamily members is controlled by Guanine nucleotide Exchange Factors (GEFs), which activate GTPases by promoting GTP for GDP exchange, and by GTPase Activating Proteins (GAPs), which stimulate their intrinsic GTPase activity, thus causing their inactivation. Some GTPases are also controlled by a third class of regulator, termed Guanine nucleotide Dissociation Inhibitors (GDIs), which can extract GTPases from membranes and maintain them in their inactive state in the cytosol. Only few GDIs have been characterized, but close to 160 human genes are predicted to encode GAPs and a similar number of GEFs may exist. An ever increasing number of proteins (currently at least 350) have been implicated as potential effectors based on their ability to interact with Ras superfamily members. Thus, over 3% of human genes may encode Ras superfamily members, their regulators or potential effectors.

The Ras superfamily is named after first human oncogene, discovered as the cellular homolog of a rat sarcoma virus transforming sequence 25 years ago. While the role

of GTPase defective Ras mutants in cancer is well understood, the medical relevance of this gene family extends well beyond Ras itself. Thus, several diseases and developmental disorders have been attributed to defects in GTPases (see accompanying table), GAPs (e.g. neurofibromatosis-1, tuberous sclerosis), GEFs (e.g. amyotrophic lateral sclerosis, Aarskog syndrome), or effector proteins (e.g. Wiskott-Aldrich syndrome, nonsyndromic X-linked mental retardation).

Members of the Ras superfamily are found in all eukaryotes and their functions are evolutionary conserved. Based on structural and functional similarities, the Ras superfamily is usually divided into the Arf, Rab, Ran, Ras, and Rho branches. The human genome predicts over 30 Arf related proteins, more than 65 Rab family members, a single Ran GTPase, about 35 Ras paralogs, and 20 Rho family members. Among major processes involving these proteins, Arf and Rab GTPases control vesicular trafficking, Ran controls the directionality of nucleocytoplasmic transport and directs mitotic spindle assembly, while Ras and Rho GTPases function in signal transduction.

Some proteins within each Ras superfamily branch have been extensively studied, while others received little attention. Among Arfs, Arf1 controls Golgi vesicle budding at least in part through its interaction with Golgi-associated adaptor protein complexes. Arf6 is located at the plasma membrane and controls actin remodeling and endocytic vesicle trafficking. Rab GTPases determine the specificity of endocytic and exocytic vesicular transport and form the largest branch of the Ras superfamily. Critical to the function of Ran in nucleocytoplasmic transport is a Ran-GDP/GTP gradient across

the nuclear membrane. This gradient reflects the opposite actions of a chromatin-associated RanGEF and a cytoplasmic RanGAP. The Ras branch includes the highly related K-Ras, K-Ras, and N-Ras isoforms, which are activated in response to a variety of extracellular signals. Active Ras in turn activates cytoplasmic signaling proteins, including Raf and PI-3 kinases. Crosstalk between GTPases is a common theme. For example, Ras interacts with RafGEFs, and multiple links have been identified between Ras and Rho GTPases. Among the latter group, RhoA, Rac1 and Cdc42 have several functions, but are best known for their roles in directing specific F-actin rearrangements.

GTP Binding Proteins (Low Molecule Weight)

	Arf	Rab	Ran	Ras	Rho
STRUCTURAL INFORMATION	Arf1 181 aa (human)	Rab1A 205 aa (human)	Ran 216 aa (human)	H-Ras 186 aa (human)	RhoA 193 aa (human)
MAMMALIAN MEMBERS	Arf 1-6 Arl 1-13 Sar1a,b Other paralogs	Rab 1-43 plus other paralogs	Ran	Ras (H-, K-, -N) R-Ras (1, 2, 3) Ral (A, B) Rap1 (a, b) Rap2 (a, b, c) Other paralogs	Rho (A, B, C) Rac (1, 2, 3) Cdc42 RhoD RhoE, Rnd2, Rnd3 Other paralogs
POST-TRANSLATIONAL MODIFICATION	Myristoylation, N-terminal acetylation	Geranylgeranylation	None	Farnesylation or geranylgeranylation, palmitoylation	Farnesylation or geranylgeranylation
INHIBITORY BACTERIAL TOXINS	Not known	Not known	Not known	Clostridium species toxins, for example <i>C. sordelli</i> lethal toxin or <i>C.</i> <i>difficile</i> toxin B-1470	Clostridium species toxins, for example or <i>C. difficile</i> toxin B-10463 (C4102) <i>C. botulinum</i> exoenzyme C3 (A9955)
ACTIVATING BACTERIAL TOXINS	Not known	Not known	Not known	Not known	<i>Escherichia coli</i> cytotoxic necrotizing factor (CNF) 1 and 2. <i>Bordetella pertussis</i> dermonecrotic toxin (DNT)
MAJOR PHYSIOLOGICAL FUNCTION	Control of Golgi vesicle budding, actin remodeling	Vesicular trafficking	Bidirectional nucleocytoplasmic transport; mitotic spindle assembly	Signal transduction	Signal transduction; actin remodeling
DISEASE RELEVANCE	Bardet-Biedl syndrome (Arl6), Lipid absorption disorders (Sar1b)	Griscelli syndrome (Rab27A)	Not known	Cancer (K-, H-, N-Ras, ARHI)	Myeloid dysfunction (Rac2)

Abbreviations

Arf : ADP ribosylation factor
Rab: Ras genes from rat brain
Ran: Ras-related nuclear
Rap: Ras-related protein
Ras: Rat sarcoma
Rho: Ras homolog

FOOTNOTES