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# Ras Family of Small GTPases In Immunity And Inflammation

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## Abstract

The Ras superfamily of small GTPases is a group of more than 150 small G proteins, all of which share some degree of homology to the founding member Ras. These small GTPases function as molecular switches within cells, impacting nearly all cellular processes. The Ras superfamily can be further divided into several smaller subfamilies, with those proteins that most closely resemble Ras belonging to the Ras subfamily. While heavily studied within the field of cancer biology, the Ras family of proteins also plays cardinal roles in immunity and inflammation. Here we review the roles of these molecular switches in regulating immune cell homeostasis and functions.

## What Are Small GTPases?

Small GTPases are molecular switches that are capable of being in an “on” state in which they are bound to **G**uanosine-**T**ri**p**hosphate (GTP), or an “off” state in which they are bound to **G**uanosine-**D**i**p**hosphate (GDP) (Figure 1). Their binding to either of these nucleotides causes changes in the conformation of the GTPase, which enables them to interact with and activate/deactivate different effector molecules. Small GTPases have an intrinsic (albeit very weak) ability to hydrolyze GTP to GDP, hence their possession of an internal “timer” which will set off eventually. More typically these switches are activated by **G**uanine-Nucleotide-**E**xchange-**F**actors (GEFs) which “exchange” GTP into a binding pocket previously occupied by GDP, hence turning “on” the GTPase. **G**TPase-**A**ctivating-**P**roteins (GAPs) activate the intrinsic GTPase activity of these proteins (speeding up the timer), and convert bound GTP into GDP and turn “off” the switch. It is the interplay between the GTPases, their GEFs and GAPs that coordinate the functioning and modulation of many diverse biological processes.

## The Ras Superfamily

Ras is a GTPase that was initially found to be mutated in a wide variety of cancers. Over time many similar GTPases were discovered to have a related 3D structure to Ras, and the family now stands at over 150 total members. This large superfamily can be further divided into at least six families; Ras, Rho, Ran, Rab, Rheb, and ARF. While each of these families of small GTPases has been extensively studied in the context of carcinogenesis, we are only beginning to scratch the surface of how these related families of proteins are able to control



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non-oncogenic processes such as immunity and inflammation. There is tremendous overlap in the functions performed by each of these families of GTPases, but the primary functions for each family are summarized in Figure 2. The Ras family, the first and most diverse of the subfamilies, can play a vital role in the regulation of immunity and inflammation.

## Ras

Ras is the founding and prototypical member of the small GTPases. It regulates multiple cellular processes including cell survival, growth, and differentiation. Upon stimulation by a growth factor or other extracellular stimuli, a receptor tyrosine kinase (RTK) activates a Ras GEF such as Son of Sevenless (SOS), which activates Ras by loading it with GTP allowing it to bind its downstream effectors (Figure 3). Following activation, Ras triggers three primary effector arms, the Raf/Mek/Erk pathway, the PI3K pathway, and the RalGDS signaling pathway. The RalGDS pathway activates Ral A and Ral B, also members of the Ras GTPase family (to be discussed below).

### ERK

When bound to Raf, Ras initiates the Raf/Mek/ERK MAPK signaling cascade. In this signaling cascade, each upstream molecule acts as a kinase to phosphorylate and activate a subsequent downstream molecule, with an eventual result being the modulation of transcription via the phosphorylation of a variety of transcription factors. ERK plays a crucial role in cell proliferation and survival. It is activated in lymphocytes downstream of TCR and BCR stimulation [1]. ERK activation can inhibit Fas-mediated apoptosis in T cells [2]. The production of the vital cytokine IL-2 by T cells is dependent upon ERK activation [3][4], as is the regulation of glucose metabolism following TCR stimulation [5]. Diacylglycerol, an important second messenger in the activation of Ras and ERK signaling, plays crucial roles in T cell responses and Fcγ receptor-mediated phagocytosis [6][7][8]. Finally, ERK signaling is also important in TLR-mediated chemokine production in dendritic cells [9].

### PI3K

Class I PI3K enzymes are composed of a regulatory (p85) and catalyitc (p110) subunit. The catalytic subunit has a Ras binding domain and can be activated by GTP-bound Ras. Upon activation, PI3K converts PIP2 to PIP3, which can serve as a docking motif for proteins containing PH domains. Within the immune system, PI3K plays crucial roles in the activation and functioning of all immune cells. PI3K regulates cytokine responsiveness and functions both in effector and regulatory T cells, and mice with PI3K deficient T cells have several immune defects [10]. The downstream PI3K target mTOR determines whether T cells become activated or undergo anergy [11]. PI3K has been shown to be crucial for signalosome formation, without which T cells have compromised antigenic responses. PI3K is also crucial for proper functioning of B cells [7][12], NK cells [13], dendritic cells (both myeloid and plasmacytoid), mast cells [14], macrophages, and neutrophils [10].

## Rap

The Rap proteins share approximately 50% sequence homology to Ras, and have an identical amino acid sequence in their effector loops. While there are multiple Rap proteins, we will only discuss here the two most well studied isoforms, Rap1a and Rap1b. It was initially hypothesized that Rap1 functioned as a direct inhibitor of Ras by competition for substrate binding. This idea has since been revised as it has become clear that Rap1 has its own set of effector proteins and exists in completely different signaling pathways than does Ras. Rap1 has been implicated in the activation of integrin-mediated adhesion [15][16], establishment of polarity [17][18], cell proliferation, and the control of cell-cell interactions

[19]. The innate immune system has a requirement for Rap1 in both macrophages [20] and dendritic cells [21]. In T cells, Rap1 is crucial for chemokine-induced polarization [19][22], and in B cells it regulates cell spreading and adhesion [23]. Rap1 is a potent activator of LFA1 [20], and at least 3 different second messengers can activate Rap: i.e., cAMP, calcium, and diacylglycerol.

## Rap1a

Due to having 90% sequence homology, Rap1a and Rap1b were traditionally assumed to serve redundant roles in the body. However experiments with knockout and transgenic mice have significantly increased our understanding of Rap1 function, as well as the specific functions carried out by Rap1a and 1b. As mentioned above Rap1a was initially thought to exist to antagonize Ras signaling. This initial hypothesis was supported by the observation that large quantities of activated Rap1a are found in anergic T cells, and that activation of CD28 by antibody binding inhibits the induction of Rap1a by TCR stimulation. Additionally in Jurkat T cells, active Rap1a expression inhibits activation of ERK and induction of IL-2 gene expression [24]. The assumption from these results was that suppression of Rap1 expression is required for a maximal T cell response. Nevertheless the theory that Rap1a inhibits lymphocyte activation has been called into question by the generation of transgenic mice expressing constitutively active Rap1a. The Rap1a transgenic mice expressing an active form of Rap1a did not have problems with either Ras signaling or T cell activation [25]. Indeed, instead of displaying an anergic response, active Rap1a-overexpressing lymphocytes possessd an enhanced TCR response. Additionally activation of Rap1a caused T cells to bind more strongly to firbronectin, and induced strong activation of B1 and B2 integrins, a process that generally requires antigen receptor binding to induce. In contrast Rap1A null mice had lymphocytes that were defective in adhesion to fibronectin and ICAM coated plates. Rap 1A null T cells showed impaired polarization following CD3 stimulation, but these mice had otherwise healthy lymphocyte function [26]. Macrophages from Rap1a knockouts had increased haptotaxis but reduced chemotaxis, and had an increase in FcR-mediated phagocytosis. Neutrophils from these mice had reduced superoxide production in response to fMLP stimulation, which is likely due to the fact that Rap1a interacts with the p22 subunit of NADPH oxidase in neutrophils [27].

## Rap1b

Since Rap1b is highly expressed in B cells, Rap1b null mice were created to understand the role of Rap1b in B cells [28]. Rap1b knockout mice showed reduced T-dependent, but normal T-independent humoral responses. B cells from these mice showed reduced migration in response to chemokines, and reduced homing to lymph nodes, while lung endothelial cells had delayed healing in a wound-healing assay [29]. These mice had fewer pre-B cells in the bone marrow, although splenic B cell proliferation was not affected. Additionally, mice have been generated that lack the Rap1 Gap SPA1 and loss of this enzyme (resulting in increased Rap1 activity) in hematopoietic and peripheral T cells resulted in antigen-induced T cell anergy. Young mice had defective T cell memory responses, and stronger Rap1 activation upon stimulation with anti-CD3 antibody. These mice had an increased rate of myeloproliferative disease and an increase in the CD44-high population of T cells. Rap1b is also the primary isoform expressed in NK cells, and may play a role in cytokine and chemokine production in these cells [30].

From these studies it is clear that, *in vivo*, Rap1 is crucial for proper functioning and development of T and B lymphocytes and that while both isoforms seem to affect chemotaxis, Rap1a has a larger effect on adhesion and neutrophil activity, while rap1b plays a crucial role in NK and humoral responses. Thus we can conclude that Rap1 is a regulator of cell adhesion, cell proliferation, and cell junction formation.

## Ral

The Ral (Ras-like) family of small GTPases is composed of two isoforms, Ral A and Ral B, which share 85% protein sequence identity between them and approximately 50% homology with Ras. Ral proteins have six known GEFs, four of which are of the RalGDS family (RalGDS, RGL1, RGL2, RGL3) and are primarily activated by upstream Ras signaling. Ral A and Ral B are highly pleiotropic and impact many diverse signaling pathways within the cell. The Ral proteins have many downstream binding partners that they interact with in order to modulate cellular conditions and respond to extracellular signals. The primary of these effectors are Ralbp1, the exocyst complex, and phospholipase D. In addition the RalGDS family itself has the capacity to act as a scaffold to activate the Ser/Thr Kinase AKT and promote cell survival and proliferation [31].

### RalBP1

Also known as RLIP76 and RIP (Ral interacting protein), RalBP1 is a non-ABC multi-functional membrane transport protein that is responsible for the majority of glutathione electrophile conjugate export in mammalian cells. This transporter is responsible for a large amount of chemotherapeutic drug removal from cancerous cells, and provides protection from a variety of forms of oxidative damage or radiation-induced stress. RalBP1 has been linked to migration, endocytosis of multiple receptor ligand pairs including TGFB, and has GAP activity towards some RHO family GTPases. Inhibition of RalBP1 with an antibody directed towards an extracellular region of the molecule induced apoptosis in target cells. Also autoantibodies to the C terminal region of RalBP1 are associated with several immune mediated diseases such as Behçet disease, SLE, and carotid atherosclerosis [32]. Ralbp1 is crucial for the proper expression of the transcription factor hsf-1, which is necessary for the expression of many heat shock proteins, which are essential for cell survival under many infectious conditions.

### Exocyst

The exocyst complex is a tethering complex that exists to tether intracellular vesicles to the plasma membrane prior to vesicular fusion during polarized exocytosis. It is an eight-member complex that exists in two parts, a three-member complex, which exists on the vesicle being trafficked, and a five-member complex that exists on the plasma membrane. Ral binds to and induces fusion between members of each of these complexes, Exo84 on the vesicular complex, and sec5 on the membrane complex. The exocyst complex plays a central role in polarized exocytosis. Additionally the exocyst has been shown to play a role in ciliogenesis, cytokinesis, wound healing, and cell migration [33]. Moreover one study has shown that the exocyst complex is needed for appropriate NK cell degranulation and proper NK cell cytotoxicity [34]. Recently it has been reported that RalB and Exo84 can assemble to autophagosomes and initiate autophagy [35]. RalB is also capable of inducing an interaction between sec5 and the non-canonical IKK TBK1, resulting in the activation of TBK1 and the downstream viral defense and survival pathways it controls [36]. A systems biology approach to assessing pieces of the drosophila phagosome identified components of the exocyst complex [37]. Being crucial for a variety of key processes involving cell polarization, the exocyst complex and its multiple components will likely be recognized to play an even more vital role within the immune system in the future.

### PLD

Phospholipase D (PLD) is an enzyme that hydrolyses phosphatidylcholine into phosphatidic acid. PLD plays an important role in the internalization and recycling of receptors. Both RalA and RalB can interact with PLD, though it is the RalA interaction with phospholipase D positively regulates Fcγ R mediated phagocytosis [38]. PLD, via phosphatidic acid

production, can activate the central kinase mTOR, and this activation can be modulated by RalA [39].

### TIPE2

Finally a recent study from our lab has shown that a crucial inflammation regulator TIPE2 operates via inhibition of the RalGDS family of GEFs (and hence Ral activity) [40].

## Conclusion

The Ras family of small GTPases plays crucial roles in many cellular processes, regulating survival, motility, polarization, attachment, proliferation, and many more. This puts them into a position of paramount importance in the proper functioning and operation of the immune system. It is anticipated that many new advances will be made in the future as we learn more about this family of molecular switches in immune cell homeostasis and function.

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## Highlights

- Discuss the role and recent thought of the role of PI3K/ERK in immunity and inflammation.
- Review the differing roles of Rap1a and Rap1b within the immune system.
- Discuss the role of the Ral and RalGDS proteins in immunity and inflammation.

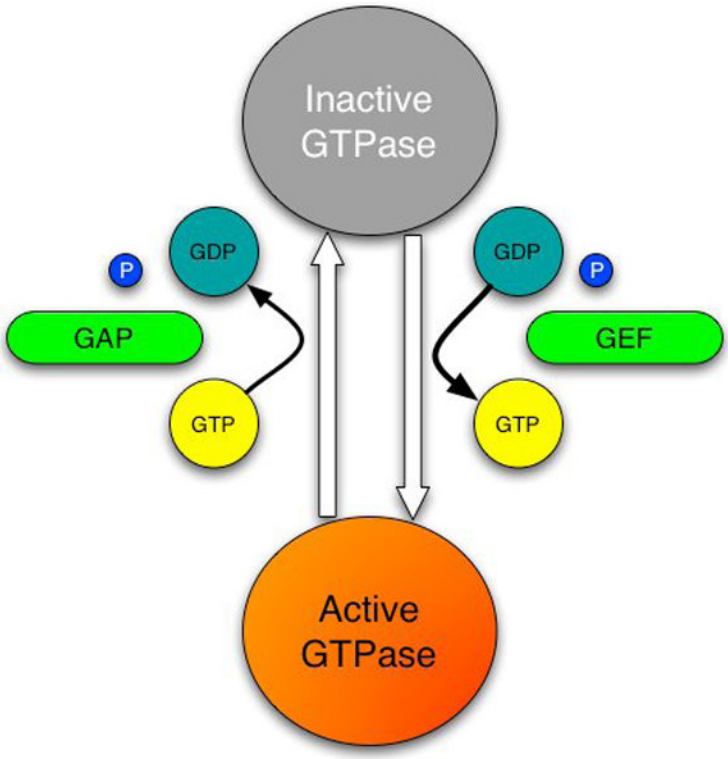


**Figure 1. Overview of GTPase signaling**

Small GTPase is “off” when bound to GDP; a GEF then removes GDP and allows GTP to bind to the GTPase, turning it “on”. All GTPases can eventually hydrolyze GTP to GDP and turn themselves off, though GAPs rapidly accelerate this process.

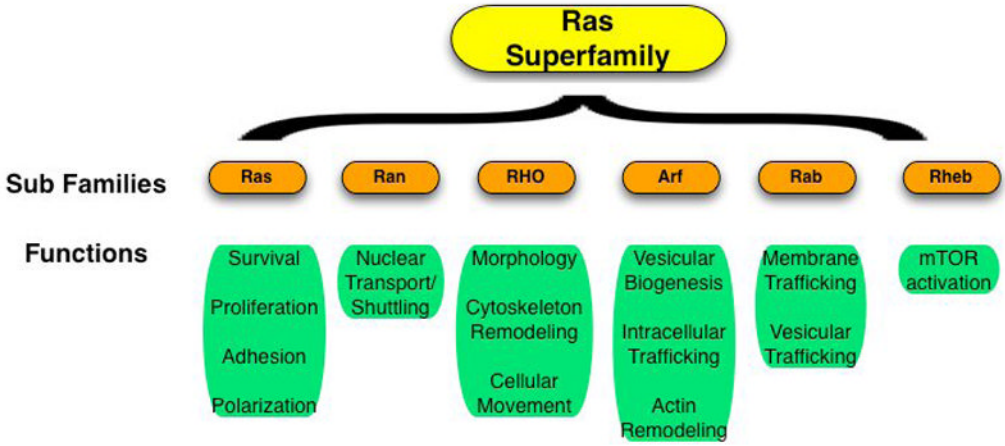


**Figure 2. The Ras Superfamily**

The Ras superfamily is broken down into 6 families, each listed with their primary functions.

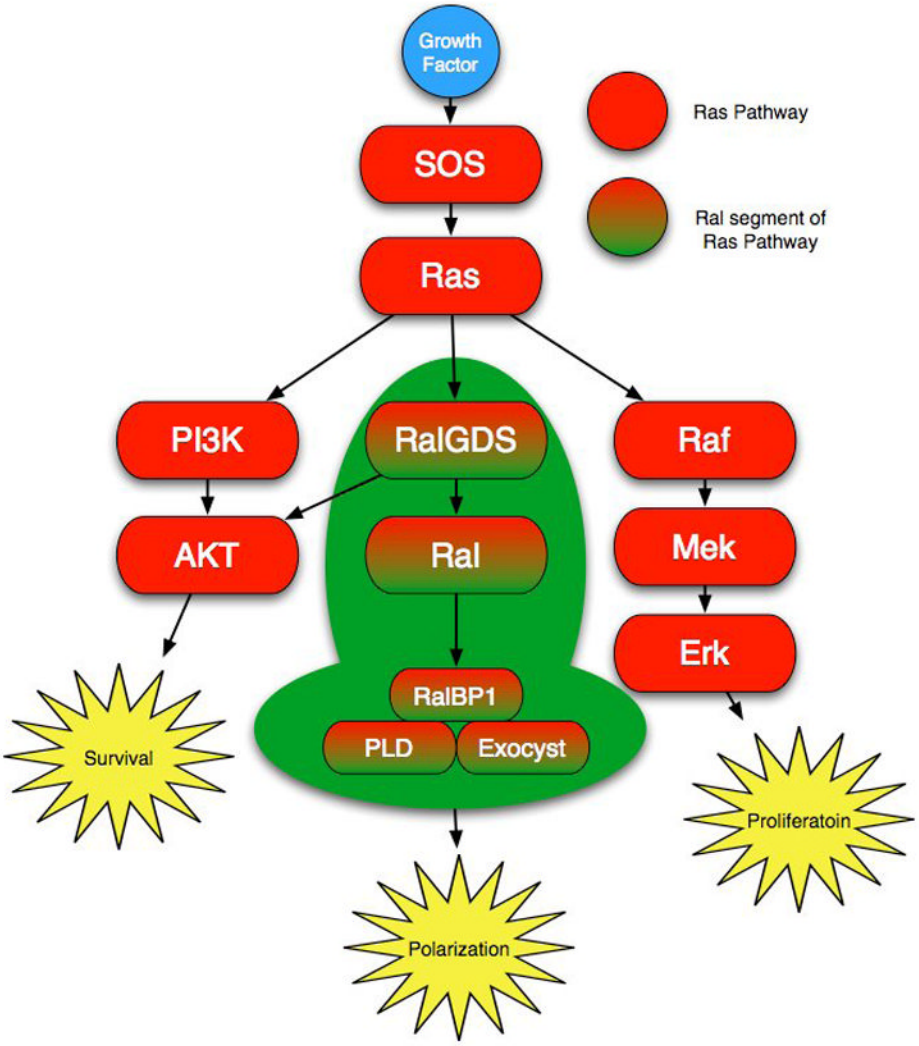


**Figure 3. Overview of Ras Signaling**

Ras signaling pathway is highlighted in Red. The Ral signaling segment of the Ras pathway is additionally marked in Green.