DOCUMENT SUMMARY

This document is a foundational scientific review from the journal *Cell*, titled "Ras and Rho GTPases: A Family Reunion." It explores the coordinated actions and "cross-talk" between two critical families of molecular switches, the **Ras** and **Rho GTPases**. The paper details how these proteins work together to control essential cellular responses like gene expression, proliferation, oncogenic transformation, and actin-based cell motility. It outlines the molecular mechanisms for this cooperation, including signal divergence (one signal activating both pathways) and convergence (both pathways targeting the same downstream machinery), highlighting the complex interplay required for normal and pathological cell behavior.

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- **Related Docs**: This paper provides specific examples of signaling molecules and pathways that are foundational to the other cell biology papers already processed (e.g., Toker_2000, Dustin_2000, Teruel_2000).

FORMATTED CONTENT

Ras and Rho GTPases: A Family Reunion

Dafna Bar-Sagi and Alan Hall

State University of New York at Stony Brook & University College London

Introduction

GTPases of the **Ras superfamily** act as molecular switches to control a wide range of essential biochemical pathways in all eukaryotic cells. Among the 60 or so that have been identified so far in mammalian cells, the **Ras** and the **Rho** families are of special interest since they couple intracellular signal transduction pathways to changes in the external environment. Like all **GTPases**, they exist in an inactive (GDP-bound) and an active (GTP-bound) conformation. **Guanine nucleotide exchange factors (GEFs)** catalyze the release of GDP, allowing GTP to bind. In their active, GTP-bound state, **Ras** and **Rho GTPases** interact with target proteins to promote a cellular response. Finally, an intrinsic GTPase activity, catalyzed further by **GTPase activating proteins (GAPs)**, completes the cycle and the **GTPase** returns to its inactive, GDP-bound state.

At least three striking features have emerged from the analysis of **Ras** and **Rho GTPases**: (1) the diversity of membrane receptors and upstream regulators that can activate these **GTPases**, (2) the diversity of cellular targets that can interact with an individual **GTPase**, and (3) the extensive cross-talk and cooperation that exists between **GTPase**-regulated signal transduction pathways. Here, we will focus specifically on the growing number of examples... of the coordinated activation and the functional cooperation between members of the **Ras** and **Rho GTPase** families in animal cells.

Molecular Mechanisms of Cross-Talk

Although diverse in nature, the molecular events identified thus far as mediators of cross-talk between **Ras** and **Rho GTPases** can be broadly classified into two mechanistic frameworks: the branching of upstream signals, referred to here as **signal divergence**, and coordinated regulation of downstream functions, referred to here as **signal convergence**.

Signal Divergence

The activation of **Ras** and **Rho GTPases** in animal cells by extracellular stimuli is mediated by **GEFs**. The **Cdc25 domain**... defines a family of **GEFs** active on members of the **Ras** family, while the **DH/PH motif**... defines a family of **GEFs**... active on the **Rho** family. There are numerous examples of this type of signal divergence.

The addition of insulin to cultured fibroblasts leads to the rapid activation of **Ras** and **Rac** and inhibition of either **GTPase** does not interfere with activation of the other. In lymphocytes, stimulation of the **T cell receptor (TCR)** appears to activate **Ras** and **Rac** independently... Such parallel activation of small **GTPases** could most obviously occur through receptor recruitment of multiple exchange factors.

Ras and **Rho GTPases** can be activated in series, such that one small **GTPase** stimulates GTP loading on another. This appears to be a common mechanism of signal divergence... **Cdc42** is a strong activator of **Rac** in many cell types, while **Rac** has been reported to activate or inhibit **Rho** to varying degrees... However, cross-talk can also occur between the two families, and constitutively activated **Ras**, for example, is a potent activator of **Rac**.

Signal Convergence

The ser/thr kinase **PAK** has emerged as a molecule that can link **Rac** and **Ras** signaling by converging on the **ERK MAP kinase** pathway. Receptor-mediated activation of **Raf**, the upstream MAP kinase kinase kinase in the **ERK** cascade, is **Ras**-dependent... **Rac** or **Cdc42** can synergize with **Raf** to promote **ERK** activation and this synergy has been reported to occur at the level of the MAP kinase kinase, **MEK1**. It turns out that **PAK**, which is a **Cdc42** and **Rac** target, can phosphorylate **MEK1**.

Another example of a molecule with the potential to connect **Ras** and **Rho GTPase** signaling pathways is **p120RasGAP**. This GTPase activating protein downregulates **Ras**, but... it has been shown that **p120RasGAP** forms a complex in cells with **p190RhoGAP**.

Biological Contexts for Cross-Talk

The existence of signaling mechanisms that link **Ras** and **Rho GTPases** argues for the physiological importance of cross-talk between these **GTPases**. This is reflected by the growing number of examples of biological responses that depend on the coordinated activation of members of both protein families.

Cell Proliferation

An important new concept to emerge from these studies is that the proliferative effects of **Ras** depend, at least under some circumstances, on signaling inputs from its relatives **Rac** and **Rho**. In quiescent rat embryo fibroblasts, expression of constitutively activated forms of **Rac** and **Raf** is sufficient to stimulate G1/S transition indicating that **Rac**- and **Raf**-dependent signals act synergistically to regulate cell cycle progression. The **Raf-MEK-ERK** cascade is responsible for the activation of **CDK4** and **CDK6**... through mechanisms involving primarily the transcriptional induction of **cyclin D1**.

Oncogenic Transformation

Evidence that the transforming activity of **Ras** requires functional **Rac** and **Rho** proteins has been provided by studies showing that dominant negative mutants of **Rac** and **Rho** inhibit **Ras**-induced transformation, and constitutively activated mutants of **Rac** and **Rho** cooperate with a constitutively activated **Raf** mutant in the induction of cellular transformation.

The Actin Cytoskeleton

The actin cytoskeleton plays an important role in defining cell shape and morphology and in orchestrating many of the dynamic aspects of cell behavior such as cell migration, axon guidance, phagocytosis, and cytokinesis. There is now abundant evidence that **Ras** and **Rho GTPases** make distinct and cooperative contributions to these processes.

> In mammalian cells, **Rac** is crucial for generating the actin-rich lamellipodial protrusions that are thought to be a major part of the driving force for movement... **Cdc42** does not appear to be required for movement itself, but instead controls polarity signals that are required for directed migration... The contribution of **Rho** to cell migration is less clear.

Ras is known to make an essential contribution to cell migration... but its role may be cell type dependent. Clearly, many biochemical details remain to be clarified, but there is little doubt that the coordinated activities of at least four small **GTPases** (**Cdc42**, **Rac**, **Rho**, and **Ras**) are required for cell migration in a variety of cell types.

Mechanisms of Signal Integration

Irrespective of the biological setting, a major mechanistic challenge posed by the combinatorial utilization of **Ras** and **Rho GTPases** is how the multiple signals that they transmit are processed coordinately to give rise to a specific physiological response.

Transcriptional Activation of the Serum Response Element

The **serum response element (SRE)** is a conserved promoter element that mediates the induction of many cellular immediate early genes following mitogenic stimulation. The activity of the **SRE** is dependent on the binding of the ubiquitous transcription factor **SRF**. In the context of the **c-fos SRE**, **SRF** forms a ternary complex with members of the family of Ets domain protein, **TCFs**... The **SRF-TCF** ternary complex is subject to regulation by converging and parallel signals from **Ras** and **Rho GTPases**, thus forming a molecular device for signal integration.

Integrin-Mediated Matrix Adhesion

Most mammalian cells are dependent on adhesion to the **extracellular matrix (ECM)** for their growth, survival, and differentiation. It is well established that the effects of the **ECM** on cellular behavior are mediated by members of the **integrin** family of cell surface adhesion molecules. The binding of **integrins** to matrix proteins triggers a variety of intracellular signaling events, including the activation of **Ras** and **Rho GTPases** (**outside-in signaling**). Activated **Ras** and **Rho GTPases** in turn regulate the extracellular binding activity of **integrins** (**inside-out signaling**).

Conclusions

The functional analysis of GTP binding proteins has most often led to the identification of a single, signal transduction pathway as being of particular importance... The identification of multiple target proteins for many of these **GTPases** (**Rac** has 12 so far) has, however, made this idea of simple linear pathways untenable and there is now little doubt that members of the **Ras** and **Rho GTPase** families each control multiple intracellular pathways.

> We have focused this review specifically on examples of cross-talk between **Ras** and **Rho GTPases** in animal cells. While the biochemical details by which this is achieved are still poorly understood, there is much experimental work that points to the importance of combinatorial activities controlled by these two families in promoting complex biological responses such as cell proliferation, cell transformation, and cell migration.