
The Complexity of the Ras Signalling Pathway

Catherine Lloyd

Table of Contents

Signal Transduction Pathway	1
Signal Transduction Pathway Diagram	2
Download This Model	3

Signal Transduction Pathway

Cardiac hypertrophy describes an abnormal condition where the heart becomes enlarged. Under stresses such as high blood pressure, or reduced blood flow through the coronary arteries, the heart must work harder. Instead of dividing and increasing in number, individual cells grow larger and genes normally expressed in the embryonic ventricle are reexpressed. Initially this compensation is effective, but excessive hypertrophy can kill more cells, which increases the stress on the heart, causing surviving cells to grow even larger, which in turn leads to an ever accelerating cycle that can eventually result in heart failure. Cardiac hypertrophy can also cause diseases such as myocardial infarction and arrhythmia, and therefore it is important to try and better understand the molecular mechanisms underlying the development of this condition.

Several *in vitro* and *in vivo* studies have suggested that a Ras-dependent signalling pathway plays a role in the regulation of cardiac hypertrophy. Ras is a low-molecular-weight GTPase which is activated by GDP-to-GTP exchange, initiated by membrane-bound receptors such as receptor tyrosine kinases (RTKs). A resting cell maintains its RTKs as inactive monomers (separate subunits). The binding of a peptide such as epidermal growth factor (EGF), or insulin to the RTKs causes them to dimerise, and this activates their kinase activities, leading to their autophosphorylation. This phosphorylation produces binding sites for proteins with src homology 2 (SH2) domains, such as growth factor receptor bound protein 2 (GRB2). GRB2, with Son of sevenless protein (SOS) bound to it, then binds to the RTK, which activates SOS. SOS is a guanine nucleotide exchange factor (GEF) which activates Ras by inducing it to release GDP and exchange it for GTP. GTPase activating proteins (GAPs) accelerate the intrinsic GTP hydrolytic activity of Ras, thereby promoting the formation of the inactive, GDP-bound form of Ras (see Figure 1 below).

Active Ras is able to stimulate many effector proteins (see Figure 2 below). These include p120 GAP, GEFs such as RalGDS, and a number of protein kinases such as phosphatidylinositol 3-kinase (PI3K), protein kinase C (PKC), mitogen-activated protein kinase kinase (MEK), mitogen-activated protein kinase kinase kinase (MEKK), c-Jun NH₂ terminal kinase (JNK), and extracellular signal-regulated kinase (ERK).

Ras is an important regulator of cell growth in all eukaryotic cells. Genetic, biochemical and molecular studies in species as diverse as *Caenorhabditis elegans* (a small nematode worm), *Drosophila* (fruit flies), and mammalian cells have all revealed that Ras has a central position in numerous signal transduction pathways that respond to diverse extracellular stimuli. Ras mediates its effects on cellular proliferation in part by activation of a cascade of kinases; Raf, MEK, and ERK. Upon activation, the ERKs phosphorylate cytoplasmic targets such as MAP kinase-interacting kinase (Mnk) and translocate to the nucleus where they activate transcription factors such as Elk-1.

The activation of Ras can trigger a diverse range of responses, including those as distinct as cell death and cell survival, depending on which effector proteins Ras interacts with. For example activation of Raf promotes apoptosis (programmed cell death), while activation of PI3K promotes cell survival. As mentioned above, several studies have also suggested that a Ras-dependent signalling pathway plays a role in the regulation of cardiac hypertrophy. Microinjection of active Ras protein into cultured cardiomyocytes increased both cell size and atrial natriuretic factor (ANF) expression (ANF levels appear to be positively correlated with hypertrophy, and it may be a protective agent).

The description of this signal transduction pathway was based on a paper by Vojtek and Der (1998), which investigates the increasing complexity of the Ras signalling pathway. The complete original paper reference is cited below:

Increasing Complexity of the Ras Signaling Pathway [http://www.jbc.org/cgi/content/abstract/273/32/19925], Anne B. Vojtek and Channing J. Ders, 1998, *The Journal of Biological Chemistry* [http://www.jbc.org/], 273, 19925-19928. (Full text [http://www.jbc.org/cgi/content/full/273/32/19925] and PDF versions [http://www.jbc.org/cgi/reprint/273/32/19925.pdf] of the article are available to subscribers on The Journal of Biological Chemistry website.)

Signal Transduction Pathway Diagram

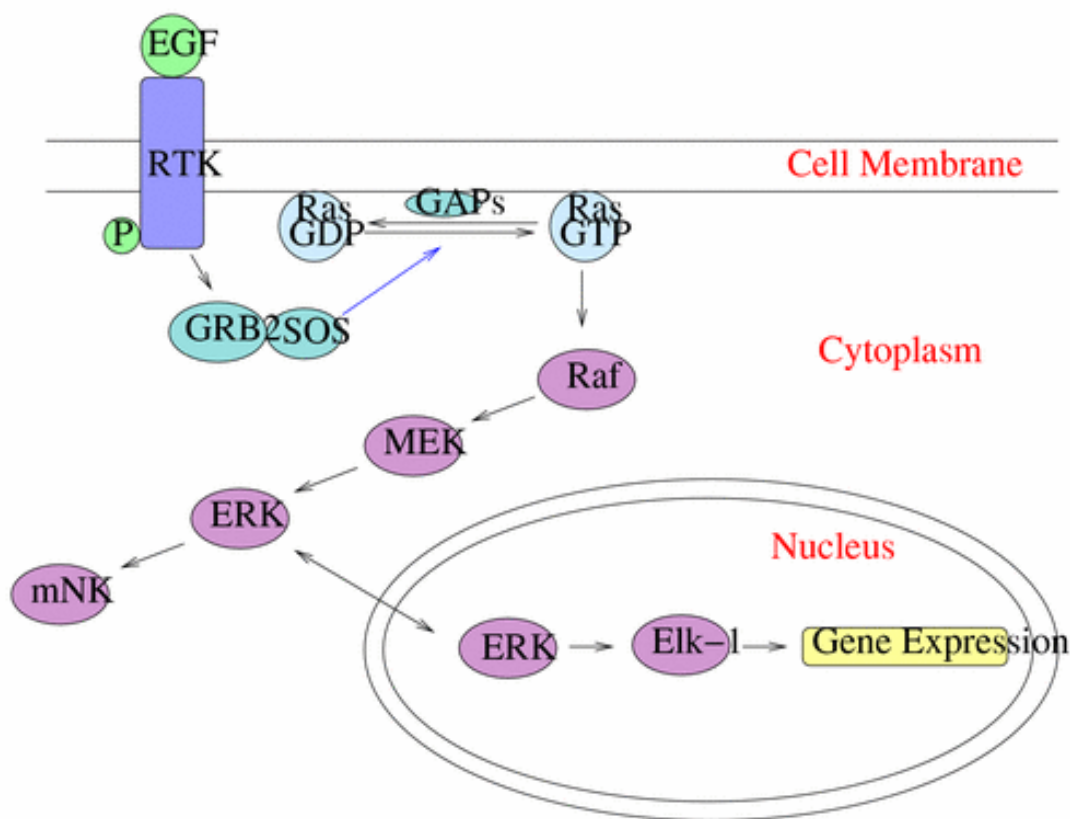


Figure 1. Schematic diagram of a Ras signalling cascade.

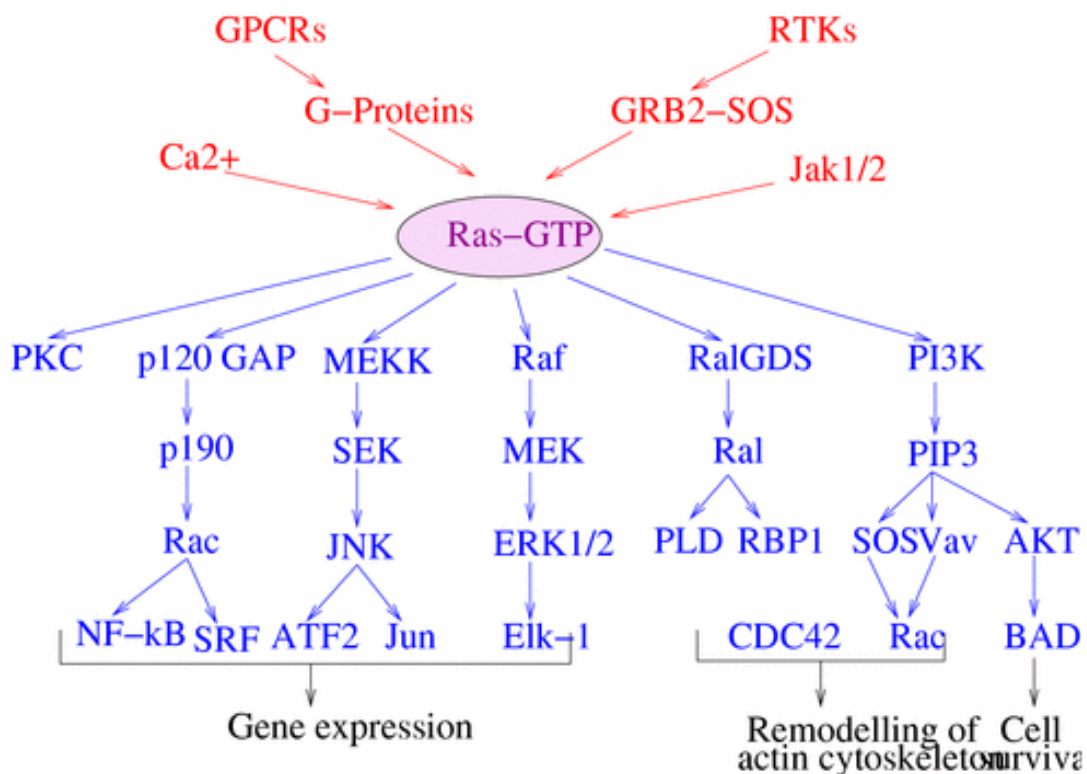


Figure 2. Schematic diagram showing some of the many Ras signalling pathways. Ras is activated through G-protein coupled receptors (GPCRs), receptor tyrosine kinases (RTKs), Janus kinase 1 (Jak), or increases in intracellular calcium (Ca²⁺). Ras targets multiple effectors (listed above).

Download This Model

- [Ras_cascade_1998.xml](#) [../models/Ras_cascade_1998.xml] — the raw XML.
- [Ras_cascade_1998.html](#) [../models/Ras_cascade_1998.html] — an HTML version for browsing online.
- [Ras_cascade_1998.pdf](#) [../models/Ras_cascade_1998.pdf] — a PDF version suitable for printing.
- [cellml_Ras_cascade_1998.tar.gz](#) [../downloads/cellml_Ras_cascade_1998.tar.gz] — a gzipped tarball with the XML and this documentation.
- [Ras_cascade_1998_maths.pdf](#) [../maths_pdf/Ras_cascade_1998_maths.pdf] — a PDF of the equations described in the model generated directly from the CellML description using the MathML Renderer [../public/tools/index.html].