

Rho Signaling: Where is the Feedback?

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ABSTRACT

The GTPase Rho forms part of a G-protein signaling system and is known to stimulate changes to the actin cytoskeleton important for cell motility responses such as cell migration, neurite outgrowth and phagocytosis. Targeting Rho signaling has been suggested as a potential route to treat a number of diseases, including cancer and heart disease [2, 4]. Several recent reviews of the Rho signaling pathway have depicted it as a feedforward cascade of interactions [1, 3], as depicted in the cartoon in Fig. 1.

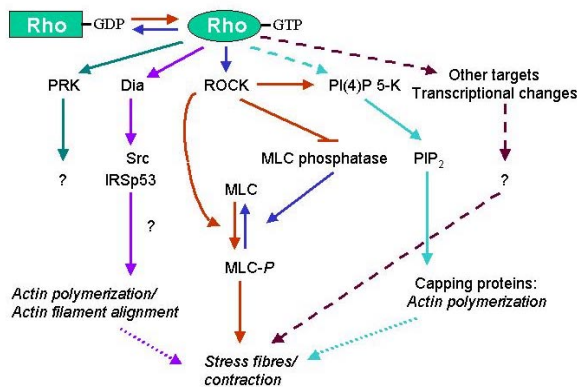


Figure 1. Rho Signaling Pathway

We modeled the central biochemical network involving Rho-Rock-MLC and MLC phosphatase interactions as a system of coupled ordinary differential equations to evaluate its behavior. The equations include kinetic parameters for which there is little experimental data. However, simulations and parameter searches carried out using Berkeley Madonna and symbolic analysis using Maple revealed that the modeled set of reactions has two stereotyped behaviors independent of any biologically reasonable set of parameter values.

First, the system is extremely sensitive to ligand activity. Even a very few molecules of ligand binding to the GPCR that activates Rho, cause the MLC to be activated to near saturation. We consider this to be unlikely in-vivo, since it would mean many cells would exhibit Rho-associated behaviors even in the absence of significant Rho activity.

Secondly, Song et al [5] report that over expression of Rho causes a decline in stress fibers, i.e. low and high levels of Rho have opposite effects. We show mathematically that the network depicted in Figure 1, is incapable of producing the effect observed by Song et al. This type of biphasic response, requires either one of the following:

- i) A negative feedback loop that negates the action of Rho signaling at high concentration of activated Rho
- ii) A delayed/threshold feed forward pathway that comes into effect at high activated_Rho concentrations and counteracts the low-Rho feedforward network.

In either case, there must be an essential interaction missing from the network illustrated in the reviews.

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