Myocyte hypertrophy: the long and winding RhoA’d

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Commentary

It seems we live in increasing complexity, and the world of signal transduction is no different. The orderly, linear pathways that just a few years ago appeared to link the cell surface to the nucleus have led to a twisting road with an array of intersecting and overlapping cascades. The fascinating study by Sah and colleagues in this issue (1) adds wonderfully to the present understanding of our location on this changing roadmap. Cardiomyocytes have a limited repertoire of responses. Faced with a number of seeming diverse insults ranging from ischemia/reperfusion, adrenergic stimulation, or hemodynamic overload, myocytes respond by undergoing cellular hypertrophy. This process appears to be repeated faithfully when neonatal myocytes in culture are exposed to a variety of ligands or mechanical forces. Several years ago, in a pioneering study from the laboratory of Ken Chien, the path by which cardiomyocytes undergo hypertrophy began to unravel. These investigators expressed an activated form of the Ras oncogene in neonatal myocytes and subsequently noted that the cells underwent a classical hypertrophic response, including the re-expression of embryonic genes such as atrial natriuretic factor (ANF), an increase in cell size, and the production of sarcomeric structures (2). Although these studies demonstrated that Ras was capable of stimulating hypertrophy, they left unanswered which proteins were downstream of Ras. Many of Ras effects in […]

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Although these studies demonstrated that Ras was capable of stimulating hypertrophy, they left unanswered which proteins were downstream of Ras. Many of Ras effects in proliferating cells result from its ability to form a molecular complex with the protein kinase c-Raf and subsequently to activate the family of mitogen-activated protein kinases (MAPK). However, it soon became clear that in cardiomyocytes, activation of MAPK could not be the sole pathway for hypertrophy. Several reports noted that activation of MAPK did not always correlate with induction of hypertrophy (3) and that expression of dominant negative forms of either c-Raf or MAPK could not completely abolish ligand-stimulated hypertrophy (4, 5). In addition, there was no evidence of increased MAPK activity in transgenic mice that overexpressed an activated Ras gene (6), although there was significant ventricular hypertrophy.

In the search for other Ras effectors, a considerable amount of attention has centered lately on the Rho family of small GTPases, a family that
includes Rac1, Cdc42, and RhoA. The interest in this family exploded after the demonstration that these proteins regulate cytoskeleton reorganization and that they synergize with Ras or Raf in growth and transformation assays (7). A role for the Rho GTPases in myocyte hypertrophy is supported by several recent studies demonstrating the effects of activated and dominant negative forms of RhoA on hypertrophic target gene expression (8–11). The effects of RhoA on the morphological aspects of hypertrophy were less clear, with recent reports giving conflicting results (9, 10). Similarly, expression of an activated form of Rac1 appeared to stimulate the hypertrophic program while expression of a dominant negative Rac gene product was inhibitory (11, 12).

In fibroblasts there is a hierarchy of small GTP-binding proteins, with Ras able to stimulate Cdc42, which can then stimulate Rac, which can in turn stimulate RhoA (7). Whether a similar hierarchy exists in other cells is unknown. Both Cdc42 and Rac can regulate the activity of c-Jun N-terminal kinases (JNK) and the p38 kinase family. Ras proteins can also weakly stimulate JNK, perhaps by activating Rac or alternatively by directly activating MEKK1 (see Figure 1). A flurry of recent reports have implicated the activation of JNK and p38 in the hypertrophic response (6, 13–17). However, recent reports have implicated the small GTPases, nature’s most versatile switches, appear to play an ever-expanding and interconnecting role in myocyte biology. Their ultimate function in hypertrophy and excitability requires further experimentation; going down that long and winding road, Sah and colleagues (1) remind us that there will undoubtedly be some wonderful twists and turns.

**Acknowledgment**

This commentary was written by the author in his private capacity. The views expressed in this article do not necessarily represent the views of NIH, DHHS, nor the United States.