Unlikely the explosive hyperplastic growth that occurs during early embryonic development, neonatal and adult cardiomyocytes undergo hypertrophy as a consequence of a much more subtle increase in the fractional growth rate of the heart. Both physiological and pathological hypertrophy results from mechanical and neurohormonal signals (and their downstream effectors) that tend to increase the rate of cardiac protein synthesis. These growth-promoting pathways are counterbalanced by signaling molecules that tend to inhibit or attenuate the prohypertrophic growth response.1 In this issue of Circulation Research, Jeong et al2 continue to add to a growing list of negative regulators of cardiomyocyte hypertrophy, and describe how PICOT (protein kinase C–interacting cousin of thioredoxin) may function to inhibit the calcineurin (CnA)–nuclear factor of activated T cells (NFAT) signaling pathway responsible for regulating specific aspects of the hypertrophic phenotype.

PICOT Is a Multidomain Scaffolding Inhibitor of Protein Kinase C-θ

PICOT was first identified in 2000 by Witte et al in a yeast 2-hybrid screen of protein kinase C (PKC)θ-interacting proteins.3 These authors used full-length, catalytically inactive PKCθ to screen a Jurkat T-cell lymphoma cDNA library. They identified a highly conserved, 37.5-kDa cytoplasmic protein containing at least 2 functional domains. The N-terminal, PKCθ binding domain shared sequence homology with the thioredoxin family of proteins but lacked the conserved Cys-Gly-Pro-Cys motif essential for enzyme activity. The C-terminal domain contained 2 tandem repeats, now called PICOT homology (PHI) domains that are shared by proteins expressed in a diverse group of organisms. PICOT formed a protein complex with PKCθ (but not PKCα) in vitro and in living cells and inhibited the PKCθ-induced activation of c-Jun N-terminal kinases but not extracellular signal-regulated kinases. This inhibitory effect was also partially dependent on CnA overexpression, suggesting an interaction among PKCθ, PICOT, and CnA in their model system. In a subsequent report, Jeong et al4 examined the potential role of PICOT as a regulator of cardiac hypertrophy.

They showed that endogenous PICOT expression increased 2-fold in the cardiomyocytes of mice subjected to transverse aortic coarctation. PICOT upregulation also occurred in cultured neonatal cardiomyocytes in response to the hypertrophic agonists phenylephrine and endothelin-1. Furthermore, transgenic overexpression of PICOT abrogated pressure overload–induced cardiac hypertrophy in vivo. Although these observations, as well as an accompanying editorial,5 focused on the potential inhibitory effects of PICOT on cardiomyocyte PKCθ, it remained unclear exactly what signaling pathways were involved. One obvious issue with the PKC dependence of the antihypertrophic effect of PICOT was the fact that mouse cardiomyocytes do not express PKCθ; therefore, the antihypertrophic effects of PICOT likely involved other mechanisms.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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625

PICOT–Muscle LIM Protein–CnA Interactions in Cardiomyocytes

Jeong et al have now returned to the question of how PICOT negatively regulates cardiac hypertrophy. Using a combination of techniques, they have shown that PICOT interacts via its C-terminal, PHI domain with muscle LIM protein (MLP) and is localized, along with the calcium-dependent phosphatase CnA, to the Z-disc of adult cardiomyocytes. When overexpressed, PICOT interfered with the interaction between MLP and CnA by competitively binding to MLP and displacing CnA from its anchorage site within the Z-disc. This displacement blocked the phenylephrine-induced increase in CnA activity and prevented the dephosphorylation and subsequent nuclear translocation of NFATc4 in cultured neonatal cardiomyocytes. A similar inhibitory effect of PICOT overexpression on CnA-dependent hypertrophic signaling was demonstrated in the previously described transgenic mice, now subjected to pressure overload. The inhibitory effect of PICOT overexpression on MLP-CnA-NFAT signal transduction could itself be prevented by overexpression of MLP, further supporting a dynamic, physical interaction among the 3 signaling molecules (Figure). Finally, the authors extend their previous observations4 by demonstrating that PICOT overexpression enhanced myofibrillar organization in neonatal cardiomyocytes and increased the velocity of fiber shortening when overexpressed in adult cells.

PICOT, MLP, and Mechanotransduction

These elegant studies have important implications and substantially advance our understanding of hypertrophic signal transduction. A key element is the interaction between PICOT and MLP. MLP belongs to a family of cysteine-rich proteins that are involved in protein–protein interactions within the cytoplasm, as well as the nucleus. MLP specifi-
Unanswered Questions

Despite these carefully performed studies, a number of questions regarding the function of PICOT in cardiomyocyte signaling remain unanswered. First, what, if any, is the role of PICOT in modulating PKC activity in cardiomyocytes? Witte et al. originally showed that PICOT binds PKCθ, a novel, Ca2+-independent PKC. However, novel (n)PKCε and nPKCθ are the major nPKC isoenzymes expressed in cardiomyocytes; therefore, it remains to be determined whether these isoforms are also inhibited by PICOT overexpression. This is an important issue, because the agonists used to elicit hypertrophy in the studies by Jeong and colleagues are also potent activators of nPKCs in neonatal and adult cardiomyocytes. Thus, it still remains to be determined to what degree the growth-inhibitory effects of PICOT overexpression are also dependent on PKC inhibition. Second, what regulates PICOT expression in cardiomyocytes? The authors have previously shown that PICOT levels increase during hypertrophy, but the responsible cellular mechanisms remain unresolved. Third, how did PICOT overexpression alter contractile function? One obvious possibility is via inhibition of PKCε-dependent phosphorylation of troponin I, but other mechanisms may be involved. However, it seems counterintuitive that a molecule that inhibits Ca2+-dependent signaling and prevents phenylephrine-induced, neonatal cardiomyocyte sarcomeric organization can also increase shortening velocity in adult cardiomyocytes. This dichotomy of structure and function in cardiomyocyte hypertrophy awaits future investigation.

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References


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