Modulating Cardiac Hypertrophy by Manipulating Myocardial Lipid Metabolism?

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The heart responds by hypertrophic growth to a variety of extrinsic stimuli, such as arterial hypertension and valvular heart disease, and to intrinsic contractile abnormalities resulting from sarcomeric gene mutations (reviewed in 1). Although it initially may serve to adapt the myocardium to increased wall tension, prolonged hypertrophy frequently results in myocyte disarray and apoptosis, as well as ventricular fibrosis, with resulting progression to heart failure and sudden death.2 A plethora of signaling cascades have been implicated in the activation of the hypertrophic gene program and cardiomyocyte growth.3 In contrast, relatively little is known about intrinsic mechanisms with the potential to inhibit or even reverse hypertrophy. The ability to harness such mechanisms offers promise in the development of novel therapeutic strategies to overcome the maladaptive consequences of hypertrophy.

Fuel generation in the adult myocardium relies on the oxidation of long chain fatty acids by the mitochondria for production of ATP. Cardiac hypertrophy is associated with a suppression of fatty acid oxidation and metabolic reversion of the heart toward increased glucose utilization, which is characteristic of the fetal heart.4 This metabolic shift can be viewed as an adaptive response, because it decreases myocardial oxygen consumption per mole of ATP generated. It is unclear at present, however, which maladaptive sequelae might result from chronically impaired oxidation of fatty acids in the heart, such as increased lipid accumulation.5

The genes involved in fatty acid oxidation are primarily regulated by a family of transcription factors that are referred to as peroxisome proliferator-activated receptors (PPARs). The three PPAR isoforms -α, -β/δ, and -γ, belong to the superfamily of nuclear hormone receptors and can be activated by diverse ligands including unsaturated fatty acids and isoform-specific drugs such as fibrates (PPARα) and antidiabetic drugs of the thiazolidinedione class (PPARγ). Whereas PPARα is highly expressed in liver and striated muscle tissue, PPARγ is most abundantly expressed in adipose tissue, the intestine, and cells of the immune system, and is expressed at substantially lower levels in heart and skeletal muscle (reviewed in 6). PPARs heterodimerize with another nuclear hormone receptor, the retinoid receptor (RXR), and recruit coactivators such as CBP/p300 to activate the transcription of target genes (Figure 1). In adipose tissue, PPARγ stimulates transcription of genes involved in lipid metabolism and promotes adipocyte differentiation.6 More recently, additional roles for PPARγ have been proposed in other tissues. In monocytes, PPARγ-dependent signaling suppresses the production of proinflammatory cytokines,7 whereas in vascular smooth muscle cells, it inhibits proliferation and migration.8,9 Targeted ablation of the PPARγ gene in genetically engineered mice results in embryonic lethality due to placental and (secondary) myocardial defects,10 whereas unchallenged heterozygous animals show no overt phenotype. However, loss of one allele of PPARγ confers protection against hyperinsulinemia and adipocyte hypertrophy when these mice are fed a high-fat diet.11

In this issue of Circulation, Asakawa et al12 describe another novel aspect of PPARγ-dependent transcription and identify it as a transducer of antihypertrophic signaling in the heart. Heterozygous PPARγ-deficient mice display an exaggerated hypertrophic response to pressure overload induced by aortic banding. Conversely, the PPARγ-agonist pioglitazone was able to blunt myocardial hypertrophy significantly in banded wild-type mice and to a lesser degree in heterozygous PPARγ-deficient mice. These findings are further supported by in vitro data indicating that angiotensin II-induced hypertrophic gene expression, as well increased cardiomyocyte size, could also be attenuated by thiazolidinediones. Similar results have also been reported recently by Yamamoto et al,13 who showed that both troglitazone and the endogenous PPARγ-ligand 15d-PGJ2 were able to block the hypertrophic phenotype and brain natriuretic peptide (BNP)—expression in cultured cardiomyocytes. Taken together, these data strongly suggest the involvement of PPARγ in a pathway for negative regulation of cardiac hypertrophy.

What could be the mechanism of the apparent antihypertrophic properties of PPARγ-signaling? First, it remains to be demonstrated that the role of PPARγ in suppression of hypertrophy solely reflects a cardiomyocyte-autonomous function. One could envision, for example, that PPARγ mutant mice also exhibit abnormalities in other cell types, such as vascular smooth muscle cells and endothelial cells, which might contribute to the sensitization to hypertrophic signals. Furthermore, insulin resistance has been implicated in the development of myocardial hypertrophy,14 suggesting that thiazolidinediones might confer a protective effect indirectly via their insulin-sensitizing properties. Clinical trials addressing this issue, however, have yielded no clear evidence for attenuated hypertrophy.15 In addition, ameliorated...

See p 1240

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insulin resistance could not account for the observed in vitro effects on cardiomyocyte hypertrophy.

Another yet unanswered question relates to the PPAR-isomerase specificity of the antihypertrophic effect. Given that PPARα is the predominant cardiac isoform and both PPARα and PPARγ have a partially overlapping ligand profile, it appears plausible that PPARα mediates similar signals in cardiomyocytes. Indeed, Kelly and coworkers have shown that PPARα expression is significantly down-regulated during pressure overload-induced cardiac hypertrophy. This was associated with the down-regulation of several key enzymes of lipid metabolism, such as carnitine palmitoyltransferase 1 (CPT-1), which controls mitochondrial fatty acid uptake. Moreover, PPARα polymorphisms appear to influence myocardial growth in response to exercise and in hypertensive patients, also supporting a role for PPARα in regulating cardiac hypertrophy. Future studies should reveal if PPARα heterozygous-deficient mice show an exacerbated hypertrophic response to pressure-overload as well.

Alternatively, PPARγ-signaling could attenuate hypertrophy by affecting pathways that are not directly involved in controlling lipid and energy metabolism. In macrophages, PPARγ-signaling has been demonstrated to negatively regulate the transcriptional response mediated by AP-1. The immediate early genes c-fos and c-jun, whose products heterodimerize to form AP-1, have previously been shown to be important in hypertrophic gene expression and could therefore serve as potential targets for PPARγ. The transcription factor NF-κB has also been demonstrated to be required for the hypertrophic response of neonatal rat cardiomyocytes in vitro. PPARγ agonists potently inhibit activation of NF-κB, suggesting a possible mechanism for their anti-hypertrophic properties. Other effectors that have previously been implicated in cardiac maladaptation and that are negatively regulated by PPARγ include endothelin-1, TNF-α, and iNOS. Interestingly, 9-cis retinoic acid, a ligand of RXR, the obligate dimerizing partner of PPARs, has also been shown to inhibit hypertrophy of primary cardiomyocytes. It remains to be seen precisely which genes within cardiomyocytes are targeted by PPARγ-signaling and if there is crosstalk or feedback with other established regulators of hypertrophy, such as adrenergic or calcineurin/NFAT pathways. The latter seems likely because PPARs are the target of several protein kinases, including protein kinase A and MAP kinases (Figure 1).

Finally, it is interesting to consider whether the recently reported antihypertrophic properties of statins, cholesteryl-ole-lowering drugs that block hepatic hydroxymethylglutaryl coenzyme A reductase, could also be mediated in part by PPARs. This fact might be suggested by the finding that statins can activate PPARα via inhibition of Rho A-signaling.

In summary, as Asakawa and coworkers point out, further studies are certainly needed to clarify the role of PPAR-dependent transcription in cardiac hypertrophy and whether it proves to be a useful therapeutic target. Moreover, it is still unclear at present to what extent myocardial growth and reprogramming of cardiac gene expression is adaptive and when it becomes detrimental. The answer to this question will direct future efforts in the prevention and treatment of cardiac hypertrophy.

### References


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