Therapeutic Challenge to Adiposity of the Heart
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The recent increase in the prevalence of obesity is one possible explanation for the adverse trends in cardiovascular morbidity and mortality. Hospitalizations for congestive heart failure have increased, and the decline in death because of coronary heart disease has leveled off. In parallel with these aspects, there is emerging evidence that inherited and acquired cardiomyopathies are associated with marked intracellular lipid accumulation in the heart.1-5 Three types of mismatches between uptake and utilization of long chain fatty acid (LCFA) lead to abnormally high intracellular LCFA concentrations in the heart, resulting in lipotoxic cardiomyopathy. First, inborn errors in myocardial β-oxidation are associated with heart failure, arrhythmias, sudden death, and pathologic lipid accumulation with a 3-fold increase in phospholipids and 100-fold increase in triglycerides in the myocardium.1 Second, myocardial metabolism switches from utilization of LCFA to utilization of glucose during the development of cardiac hypertrophy and in the ischemic and failing heart. Although this metabolic switch initially serves an adaptive function, accumulation of intracellular LCFA in these acquired conditions contributes to contractile dysfunction and the generation of cardiac arrhythmias.2 Third, several-fold increased cardiac myocyte triglyceride stores are observed in animal models of obesity and diabetes, in which high serum free fatty acid levels promote LCFA uptake in excess of tissue capacity for utilization.3,4 This lipid accumulation contributes to cardiac myocyte apoptosis by nonoxidative metabolic pathways, such as ceramide synthesis, and to congestive heart failure (Figure). Even in humans, myocardial lipid content has been recently reported to increase with the degree of adiposity and contribute to the adverse structural and functional cardiac adaptations, suggesting that myocardial lipid content is a biomarker and putative therapeutic target for cardiac disease in obese patients.5 Indeed, one trial of the medium-chain triglyceride-enriched diet rescued the baseline ventricular function of lipotoxic cardiomyopathy mice and provided a rationale for serum lipid-lowering strategies in the treatment of diabetic cardiomyopathy.6

CD36, a member of the class B scavenger receptors, is a highly glycosylated, single chain 88-kDa protein that binds oxidized low density lipoprotein (LDL), fatty acids, anionic phospholipids such as phosphatidylinositol and phosphatidylserine, and the proteins collagen and thrombospondin.7 As a result of the broad ligand specificity, multiple roles of CD36 have been demonstrated. In vitro and in vivo studies indicate that a significant proportion of binding and internalization of oxidized LDL by macrophages occurs through CD36.8 CD36 is involved in the differentiation of monocytes and accumulation of lipid in macrophages after exposure to oxidized LDL. In addition to its role as a scavenger receptor, CD36 is one of the four proteins that function as LCFA transporters and facilitate uptake of LCFA in adipocytes, epithelia, and cardiac and skeletal muscles. The expression of CD36 correlates with tissue activity of fatty acid metabolism.9 CD36 is upregulated, together with LCFA uptake, by muscle contraction and is increased in the muscle of diabetic mice and those fed by a high fat diet.10 All of CD36, fatty acyl-CoA synthetase 1 (ACS1), lipoprotein lipase, and fatty acid transport protein (FATP)-1 serve as LCFA transporters in the heart, and function coordinately with each other to regulate lipid homeostasis in tissues. Cardiac overexpression of LCFA transporters such as glycosylphosphatidylinositol-anchored lipoprotein lipase,11 FATP-1,12 and long-chain ACS1,13 and of peroxisome proliferator-activated receptor (PPAR) α13 each leads to lipid accumulation in the myocardium that is associated with systolic or diastolic ventricular dysfunction. PPARα is a critical regulator of myocardial fatty acid uptake and utilization, and activation of cardiac PPARα regulatory pathways results in a reciprocal repression of glucose uptake and utilization pathways, and derangements in myocardial energy metabolism typical of the diabetic heart.14 In insulin-deficient and insulin-resistant forms of diabetes mellitus, the cardiac PPAR-α regulatory pathway and downstream genes have been reported to be upregulated.13

The current study by Yang et al is an important step in searching the therapeutic strategies for lipotoxic cardiomyopathy.14 The authors investigated the role of the LCFA transporter CD36 in the pathophysiology of lipotoxic forms of cardiomyopathy and the possibility for the prevention or treatment of cardiac dysfunction related to obesity and diabetes. They used mice with cardiac-restricted overexpression of PPAR-α which were characterized by excessive lipid accumulation in the myocardium and ventricular dysfunction. To define the therapeutic possibility of the blockade of cellular LCFA import, myosin heavy chain (MHC)-PPARα transgenic mice were crossed with mice deficient for CD36 and the cardiomyopathic phenotype was analyzed. They showed that CD36-deficiency prevented myocyte LCFA accumulation and completely rescued the lipotoxic cardiomyopathy of MHC-PPARα mice as expected. However, the activation of PPARα target genes involved in myocardial fatty acid oxidation pathways in the hearts of MHC-PPARα mice was unchanged in the CD36-deficient background, and
moreover, PPARα-mediated suppression of genes involved in glucose uptake and oxidation was reversed in the MHC-PPARα/CD36−/− mice. They concluded that CD36 is necessary for the development of lipotoxic cardiomyopathy in MHC-PPARα mice and that novel therapeutic strategies aimed at reducing CD36-mediated fatty acid uptake show promise for the prevention or treatment of cardiac dysfunction related to obesity and diabetes.

CD36 deficiency reversed the increased levels of esterified palmitic, stearic, oleic, and linoleic acids, which are enriched in the high fat chow, in the hearts of MHC-PPARα mice. However, cardiac expression of the FATP1 gene, one kind of LCFA transporter, remained modestly elevated in the MHC-PPARα mice. In addition, the CD36-deficiency study showed that CD36 plays a rate-limiting role in the transport step greater than 60% but not completely in the heart. Therefore, future loss-of-function studies aimed at each of the other cellular transport proteins alone and in combination with CD36 deficiency will be necessary to further define the physiological role, relevant interactions among the fatty acid transporters, and therapeutic targets for prevention and treatment of cardiac dysfunction related to obesity and diabetes.

Despite functional rescue, fatty acid oxidation rates were not significantly reduced in the MHC-PPARα/CD36−/− hearts compared with HMC-PPARα hearts. In contrast, the CD36-deficient background reversed the reduction in glucose oxidation rates in MHC-PPARα hearts, being associated with the normalization of GLUT4 and the negative regulator of glucose oxidation, pyruvate dehydrogenase kinase 4. Mean glucose oxidation rates in the MHC-PPARα/CD36−/− hearts were increased by 5-fold to levels of the CD36−/− hearts. CD36 is an important factor in the metabolic adaptation to diet.13 Whereas CD36 deficiency predisposes to insulin resistance induced by high fructose, it partially protects from insulin resistance induced by high-fat diets and enhances insulin responsiveness on a high-starch, low-fat diet. The mechanism underlying the linkage of CD36 deficiency and relief from the suppression of myocardial glucose uptake and oxidation is necessary to be elucidated. It is also of importance how fatty acid oxidation is maintained in the hearts of MHC-PPARα/CD36−/− mice, when less LCFA is delivered in the absence of CD36. This is an unanswered question.

As an adverse effect, the authors show that serum cholesterol levels were slightly but significantly higher in two CD36-deficient groups. CD36 null animals have been reported to show a significant increase in fasting levels of cholesterol, nonesterified free fatty acids, and triacylglycerol.16 The increase in cholesterol is mainly within the high density lipoprotein fraction, whereas the increase in triacylglycerol is within the very low density lipoprotein fraction. The long-term effect of this kind of dyslipidemia on cardiovascular events needs to be examined. The biventricular-to-body weight ratio of two-month-old male CD36−/− mice was mildly but significantly increased compared with that of the wild-type mice fed standard or high fat chow for four weeks, despite the fact that the absence of CD36 rescued the cardiac function. An association between CD36 deficiency and hereditary hypertrophic cardiomyopathy has been reported in humans and linked to impaired uptake of LCFA by the myocardium.17 Chronically, cardiac hypertrophy exacerbates diastolic dysfunction and leads to congestive heart failure. This is also an important issue to be resolved before the establishment of CD36 deficiency as a treatment strategy. The expression of mitochondrial uncoupling protein (UCP) 2 and 3, known PPARα target genes, was activated to a similar extent in the hearts of MHC-PPARα and MHC-PPARα/CD36−/− mice, suggesting that respiratory uncoupling was adaptively increased in the heart of the MHC-PPARα/CD36−/− mice. UCP2 in macrophages was reported to decrease reactive oxygen species and atherosclerosis,18 whereas UCP1 in aortic smooth muscle cells causes hypertension and increases diet-induced atherosclerosis, being associated with increased superoxide production and decreased availability of nitric oxide.19 The outcome of long-term respiratory uncoupling remains to be elucidated.

In the treatment of lipotoxic cardiomyopathy, a potential role of CD36 deficiency seems to be expected. Nevertheless,
careful studies are needed to explore the precise mechanisms for any benefits as well as to identify undesirable effects. By identifying the significant benefits of CD36-deficiency, the authors have shown one of the therapeutic challenges for adiposity of the heart.

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