The pandemic of obesity is transforming industrialized societies. Presently, more than one third of US adults (≈80 million) are obese, predisposing them to a wide range of disorders. Chief among them is type 2 diabetes mellitus. Indeed, diabetes mellitus affects >300 million people worldwide, and this number is expected to continue to grow. In the United States alone, diabetes mellitus affects 29 million people, accounting for an enormous burden to both individuals and our healthcare infrastructure.2

Causes are multifactorial because diabetes mellitus predisposes to a wide range of comorbidities. These include hypertension, atherosclerotic cardiovascular disease, and cancer. Above and beyond that, the diabetic milieu itself is toxic to the heart; circulating hormones and cytokines, alterations in adrenergic tone, increases in free fatty acids, and hyperglycemia conspire to elicit untoward effects on the heart. Structural and functional abnormalities of the myocardium, beyond that elicited by ischemia or hypertension, have been emphasized and called diabetic cardiomyopathy.4

Diabetic cardiomyopathy is marked by left ventricular hypertrophy, fetal gene reactivation, and lipid accumulation in cardiomyocytes, which together promote contractile dysfunction.5 A landmark study in 2002 by Finck and colleagues6 shed light on the transcriptional mechanisms of diabetic cardiomyopathy. These investigators reported that the transcription factor peroxisome proliferator-activated receptor-α (PPARα), along with its transcriptional targets, is upregulated in hearts in preclinical models of diabetes mellitus. Cardiomyocyte-restricted overexpression of PPARα led to increases in fatty acid oxidation and reductions in glucose use, a pattern typical of diabetes mellitus. Phenotypically, PPARα transgenic mice manifested ventricular hypertrophy, contractile dysfunction, and accumulation of lipids within cardiomyocytes. In summary, the cardiac phenotype induced by PPARα overexpression mimics clinical features of human disease. To date, however, mechanisms governing the upregulation of PPARα in the diabetic heart have remained elusive.

In this issue of Circulation, Liu et al7 describe a novel upstream regulator of PPARα, a ubiquitin ligase called MG53 (mitsugumin 53). These investigators show that this protein, also known as TRIM72, governs expression of the gene coding for PPARα. Its abundance is increased in models of diabetes mellitus, and it triggers a cascade of events that contribute to heart disease.

MG53 is a member of the so-called tripartite motif family. The protein, which is expressed exclusively in skeletal and cardiac muscle, harbors an N-terminal TRIM motif with Ring, B-box, and coiled-coil moieties, as well as C-terminal SPRY domain.8 Prior work has demonstrated that MG53 plays critical roles in myogenesis, vesicle trafficking, and membrane repair.9,10

The intrinsic E3 ligase activity of MG53 prompted researchers to identify endogenous targets. Prominent targets include the insulin receptor and insulin receptor substrate-1, critical molecules in the insulin signaling cascade.11,12 This intimate connection between MG53 and elements of the insulin cascade suggested, in turn, that MG53 participates in metabolic regulation. Indeed, these investigators reported previously that MG53 is substantially upregulated in skeletal muscle in preclinical models of diabetes mellitus.12 Genetic silencing of MG53 promoted metabolic improvements and amelioration of insulin resistance. Furthermore, this group reports now that MG53 is robustly induced in hearts under conditions of diabetes mellitus.7

In the present report, Liu et al set out to define the role of MG53 in diabetes mellitus–associated cardiomyopathy using a model of cardiomyocyte-restricted forced expression of MG53. Adult MG53 transgenic mice manifested profound cardiac hypertrophy, reactivation of the fetal gene program, cardiomyocyte steatosis, and contractile dysfunction, all reminiscent of diabetic cardiomyopathy. Consistent with a role for MG53 in suppressing insulin signaling, these investigators found that both the insulin receptor and insulin receptor substrate-1 are significantly reduced and that insulin-stimulated Akt phosphorylation is attenuated. These molecular events elicit alterations in nutrient metabolism in the myocyte, including increases in fatty acid oxidation and declines in glucose use, established features of diabetic heart disease.

These investigators went on to dissect mechanisms whereby MG53 overexpression triggers pathological changes. For one, they used RNA-seq to define global alterations in the transgenic hearts, uncovering significant activation of the PPARα signaling pathway. As an important correlative observation,
they note that MG53 induction is accompanied by upregulation of PPARα under various diabetic conditions. To probe for a possible mechanistic link between these events, the authors conducted loss-of-function and gain-of-function studies in vitro that together firmly established PPARα as a downstream target of MG53. Additionally, MG53 proved to be sufficient to activate the PPARα gene promoter in a luciferase assay, and chromatin immunoprecipitation assays suggest that the protein is recruited to the promoter. Finally, MG53 not only stimulated PPARα expression but also augmented levels of PPARα targets. Functionally, MG53-induced lipid uptake in cardiomyocytes is critically dependent on PPARα because knockdown of PPARα strongly attenuated lipid accumulation.

As with any important study, this one raises new and interesting questions. Diabetes mellitus is typically associated with elevations in circulating glucose, free fatty acids, and various hormones and cytokines. Cardiac uptake of fatty acids is increased, which is associated with impairment of glucose use. When the capacity of the myocyte for fatty acid oxidation does not rise commensurately with increases in fatty acid uptake, lipid accumulation ensues. This steatosis is cytotoxic and compromises contractile function. Fasting in obese Zucker rats leads to accumulation of myocardial lipid above that seen in wild-type controls, likely a result of dyssynchronization between the availability and oxidation of fatty acids. Furthermore, adipose triglyceride lipase deficiency causes depletion of the activating lipid ligand of PPARα, coupled with excessive lipid accumulation in cardiomyocytes. Pharmacological activation of PPARα to stimulate lipid oxidation can effectively reverse this pathological phenotype. It is possible that MG53 preferentially increases fatty acid uptake without sufficiently stimulating oxidation, which would be a maladaptive turn of events in the cardiomyocyte.

Insulin is a major anabolic hormone. It is not surprising then that diabetes mellitus, a state of absolute or relative insulin resistance, is marked by activation of catabolic events. Indeed, as a general rule, catabolic pathways such as the ubiquitin-proteasome system are activated in diabetes mellitus, and defining the pathways are activated in diabetes mellitus, and defining the role of MG53 described here do not fit neatly into either of these categories. In the future, it will be of great interest to define precise mechanisms whereby MG53 regulates expression of the gene coding for PPARα.

Disclosures
None.
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Diabetic Cardiomyopathy: Catabolism Driving Metabolism
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