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.

Diabetic cardiomyopathy is marked by left ventricular hypertrophy, fetal gene reactivation, and lipid accumulation in cardiomyocytes, which together promote contractile dysfunction. A landmark study in 2002 by Finck and colleagues 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 under conditions of diabetes mellitus. Genetic silencing of MG53 overexpression triggers pathological changes. For one, MG53 overexpression triggers pathological changes. For one, adult MG53 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 al 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 a C-terminal SPRY domain. Prior work has demonstrated that MG53 plays critical roles in myogenesis, vesicle trafficking, and membrane repair.

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. 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. Genetic silencing of MG53 prompted metabolic improvements and amelioration of insulin resistance. Furthermore, this group reports now that MG53 is robustly induced in hearts under conditions of diabetes mellitus.

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 dysynchronisation 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. In this report, we learn that an element within a major catabolic cascade, the ubiquitin-proteasome system, actually promotes pathogenesis of diabetic cardiomyopathy.

In the case of type 2 diabetes mellitus, however, the situation is more complex. In end-stage disease, pancreatic β cells are depleted, and circulating insulin is low. At earlier points in disease progression, however, high levels of circulating insulin are seen, and the effects in different tissues are variable. For example, insulin resistance in type 2 diabetes mellitus increases hepatic lipid synthesis, as would be expected. Seemingly paradoxically, however, it does not suppress glucose production in liver. In muscle, glucose uptake is indeed impaired. This so-called selective insulin resistance remains a puzzle. Nevertheless, in the majority of instances, catabolic pathways are activated in diabetes mellitus, and defining the role of MG53 in these tissues will be important.

This study falls in line with an existing literature pointing to regulated mechanisms of protein degradation governing the action of transcription factors. In the most conventional cases, the ubiquitin-proteasome system degrades a transcription factor (decreasing activity) or an inhibitor (increasing activity). In some instances, a “used” transcription factor bound to DNA is degraded to allow “fresh” molecule to bind, an “activation by destruction” event. Interestingly, the actions of MG53 described here do not fit neatly into either of these categories.

An E3 ligase can sometimes promote transcriptional activity independently of ligase activity. Other times, they govern gene transcription via monoubiquitination, a reaction that does not target substrate for degradation. Ubiquitination can also promote the binding of a transcription factor to DNA. For example, monoubiquitination of FoxO4 promotes nuclear translocation, thereby enhancing transcriptional activity; deubiquitination reverses this process. Again, the actions of MG53 described here do not fit neatly into any 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.

Multiple lines of evidence point to MG53 as an essential component of the membrane repair machinery. Deficiency of MG53 leads to exacerbated loss of mitochondrial membrane potential and cell death triggered by ischemia/reperfusion. Moreover, MG53 constitutes a primary determinant of both ischemic preconditioning and postconditioning triggered by prosurvival pathways. Heterologous expression of recombinant human MG53 confers robust cytoprotection in heart, lung, and skeletal muscle in the settings of a variety of stress conditions. The present study, however, highlights that caution must be exercised when contemplating translational strategies to activate MG53. Perhaps an ideal therapeutic approach is one that selectively inhibits the E3 ligase activity of MG53 while enhancing its membrane repair properties. Further work is needed to parse these diverse functions of MG53.

Diabetic heart disease is a large and growing public health hazard. The report by Liu et al unveils a novel and potentially important mechanism of the pathogenesis of this disease. Their work raises the possibility that MG53 contributes to adverse events in heart by the concerted actions of 2 processes: targeted degradation of elements within the insulin signaling cascade and specific upregulation of PPARα, thereby dismantling the metabolic handling of both glucose and lipids.

As we enter the age of “diabetocardiology,” studies such as this are urgently needed. These investigators are to be congratulated for their ground-breaking mechanistic work at the leading edge of a worldwide pandemic of diabetes mellitus and heart disease.

Acknowledgments

We thank the members of the Hill laboratory for constructive comments.

Sources of Funding

This work was supported by grants from the National Institutes of Health (HL-120732; HL-100401), American Heart Association, (14SFRN20670003 and 14SFRN20510023), Cancer Prevention and Research Institute of Texas (RP110486P3), and Leducq Foundation (11CVD04). Dr Wang was supported by a Scientist Development Grant from the American Heart Association (14SDG18440002).

Disclosures

None.
References


Key Words: Editors | diabetic cardiomyopathies | metabolism
Diabetic Cardiomyopathy: Catabolism Driving Metabolism
Zhao V. Wang and Joseph A. Hill

Circulation. 2015;131:771-773; originally published online January 30, 2015;
doi: 10.1161/CIRCULATIONAHA.115.015357
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/131/9/771

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/