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Diabetic Cardiomyopathy: Catabolism Driving Metabolism

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The pandemic of obesity is transforming industrialized societies. Presently, more than one-third of U.S. adults (≈ 80 million) are obese, predisposing them to a wide range of disorders. Chief among them is type 2 diabetes mellitus. Indeed, diabetes affects over 300 million people worldwide, and this number is expected to continue to grow.¹ In the US alone, diabetes affects 29 million people, accounting for an enormous burden to both individuals and our healthcare infrastructure.²

Patients with diabetes are at 2–4 times increased risk of developing heart disease.³ Indeed, the primary cause of mortality in patients with diabetes is cardiovascular disease, accounting for 50–80% of deaths.

Causes are multifactorial, as diabetes predisposes to a wide range of comorbidities. These include hypertension, atherosclerotic cardiovascular disease, and cancer. Above and beyond that, the diabetic “milieu” 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, above and beyond that elicited by ischemia or hypertension, has been emphasized and termed “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 Kelly and colleagues shed light on transcriptional mechanisms of diabetic cardiomyopathy.⁶ These investigators reported that the transcription factor PPAR α , along with its transcriptional targets, is up-regulated in hearts from preclinical models of diabetes. Cardiomyocyte-restricted over-expression of PPAR α led to increases in fatty acid oxidation and reductions in glucose utilization, a pattern typical of diabetes. Phenotypically, PPAR α transgenic mice manifested ventricular hypertrophy, contractile

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dysfunction and accumulation of lipids within cardiomyocytes. In sum, the cardiac phenotype induced by PPAR α over-expression mimics clinical features of human disease. To date, however, mechanisms governing the up-regulation of PPAR α in diabetic heart have remained elusive.

In this issue of *Circulation*, Liu et al describe a novel upstream regulator of PPAR α , a ubiquitin ligase named MG53 (mitsugumin 53).⁷ These investigators show that this protein, also known as TRIM72, governs expression of the gene coding for PPAR α . Its abundance is increased in models of diabetes, 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, and a C-terminal SPRY domain.⁸ Prior work has demonstrated that MG53 plays critical roles in myogenesis, vesicle trafficking, and membrane repair.⁸⁻¹⁰

The intrinsic E3 ligase activity of MG53 prompted researchers to identify endogenous targets. Prominent ones include the insulin receptor and IRS-1 (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 up-regulated in skeletal muscle in preclinical models of diabetes.¹² Genetic silencing of MG53 promoted metabolic improvements and amelioration of insulin resistance. Further, they report now that MG53 is robustly induced in hearts under conditions of diabetes.⁷

In the present report, Liu et al set out to define the role of MG53 in diabetes-associated cardiomyopathy, employing 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 IRS-1 are significantly reduced and insulin-stimulated Akt phosphorylation attenuated. These molecular alterations elicit alterations in nutrient metabolism in the myocyte, including increases in fatty acid oxidation and declines in glucose utilization, established features of diabetic heart disease.

These investigators went on to dissect mechanisms whereby MG53 over-expression triggers pathological changes. For one, they employed RNA-seq to define global alterations in the transgenic hearts, uncovering significant activation of the PPAR α signaling pathway. As an important correlative observation, they note that MG53 induction is accompanied by up-regulation of PPAR α under various diabetic conditions. To probe for a possible mechanistic link between these events, the authors conducted loss- and gain-of-function studies *in vitro* which together firmly established PPAR α as a downstream target of MG53. Additionally, MG53 proved to be sufficient to activate the PPAR α gene promoter in a luciferase assay, and ChIP assays suggest that the protein is recruited to the promoter. Finally, MG53 not

only stimulated PPAR α expression but also augmented levels of PPAR α targets. Functionally, MG53-induced lipid uptake in cardiomyocytes is critically dependent on PPAR α , as knockdown of PPAR α strongly attenuated lipid accumulation.

As with any important study, this one raises new and interesting questions. Diabetes 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 utilization. When the myocyte's capacity for fatty acid oxidation does not rise commensurate with increases in fatty acid uptake, lipid accumulation ensues. This steatosis is both 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.¹³ Further, adipose triglyceride lipase deficiency causes depletion of PPAR α 's activating lipid ligand coupled with excessive lipid accumulation in cardiomyocytes. Pharmacological activation of PPAR α to stimulate lipid oxidation can effectively reverse this pathological phenotype.¹⁴ 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, 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 (UPS), are activated in diabetes. In this report, we learn that an element within a major catabolic cascade, the UPS, actually promotes pathogenesis of diabetic cardiomyopathy.

In the case of type 2 diabetes, however, the situation is more complex. In end-stage disease, pancreatic beta 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 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"¹⁵ remains a puzzle going forward. Nevertheless, in the majority of instances, catabolic pathways are activated in diabetes, and it will be important to define the role of MG53 in these tissues.

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 UPS degrades a transcription factor (decreasing activity), or it degrades 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.¹⁶ Interestingly, the actions of MG53 described here do not fit neatly into either of these categories.

An E3 ligase can sometimes promote transcriptional activity independent of ligase activity.¹⁷ 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.¹⁸ For example, monoubiquitination of FoxO4 promotes

nuclear translocation, thereby enhancing transcriptional activity; deubiquitination reverses this process.¹⁹ Again, the actions of MG53 described here do not fit neatly into any of these categories. Looking to the future, it will be of great interest to define precise mechanisms whereby MG53 regulates expression of the gene coding for PPAR α .

Multiple lines of evidence point to MG53 as an essential component of the membrane repair machinery.^{8, 10} Deficiency of MG53 leads to exacerbated loss of mitochondrial membrane potential and cell death triggered by ischemia/reperfusion.²⁰ Moreover, MG53 constitutes a primary determinant of both ischemic preconditioning and post-conditioning triggered by pro-survival pathways.^{21, 22} Heterologous expression of recombinant human MG53 confers robust cytoprotection in heart²³, lung²⁴, and skeletal muscle²⁵ 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 MG53's E3 ligase activity 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 pathogenesis in this disease. Their work raises the possibility that MG53 contributes to adverse events in heart by the concerted actions of two processes: targeted degradation of elements within the insulin signaling cascade and specific up-regulation of PPAR α , 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 pathbreaking mechanistic work at the leading edge of a worldwide pandemic of diabetes and heart disease.

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References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27:1047–1053. [PubMed: 15111519]
2. Association AD. Economic costs of diabetes in the u.S. In 2012. *Diabetes Care*. 2013; 36:1033–1046. [PubMed: 23468086]
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres J, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics-2015 update: A report from the American heart association. *Circulation*. 2015; 131:e29–e322. Epub 2014 Dec 17. 10.1161/CIR.000000000000152 [PubMed: 25520374]

4. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia*. 2014; 57:660–671. [PubMed: 24477973]
5. Battiprolu PK, Hojaye B, Jiang N, Wang ZV, Luo X, Iglewski M, Shelton JM, Gerard RD, Rothermel BA, Gillette TG, Lavandero S, Hill JA. Metabolic stress-induced activation of foxo1 triggers diabetic cardiomyopathy in mice. *J Clin Invest*. 2012; 122:1109–1118. [PubMed: 22326951]
6. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X, Gross RW, Kozak R, Lopaschuk GD, Kelly DP. The cardiac phenotype induced by pparalpha overexpression mimics that caused by diabetes mellitus. *J Clin Invest*. 2002; 109:121–130. [PubMed: 11781357]
7. Liu F, Song R, Feng Y, Guo J, Chen Y, Zhang Y, Chen T, Wang Y, Huang Y, Li C-Y, Cao C, Zhang Y, Hu X, Xiao R-P. Upregulation of mg53 induces diabetic cardiomyopathy via transcriptional activation of ppar-alpha. *Circulation*. 2015; 131:XX–XXX.
8. Cai C, Masumiya H, Weisleder N, Matsuda N, Nishi M, Hwang M, Ko JK, Lin P, Thornton A, Zhao X, Pan Z, Komazaki S, Brotto M, Takeshima H, Ma J. Mg53 nucleates assembly of cell membrane repair machinery. *Nat Cell Biol*. 2009; 11:56–64. [PubMed: 19043407]
9. Lee CS, Yi JS, Jung SY, Kim BW, Lee NR, Choo HJ, Jang SY, Han J, Chi SG, Park M, Lee JH, Ko YG. Trim72 negatively regulates myogenesis via targeting insulin receptor substrate-1. *Cell Death Differ*. 2010; 17:1254–1265. [PubMed: 20139895]
10. Cai C, Masumiya H, Weisleder N, Pan Z, Nishi M, Komazaki S, Takeshima H, Ma J. Mg53 regulates membrane budding and exocytosis in muscle cells. *J Biol Chem*. 2009; 284:3314–3322. [PubMed: 19029292]
11. Yi JS, Park JS, Ham YM, Nguyen N, Lee NR, Hong J, Kim BW, Lee H, Lee CS, Jeong BC, Song HK, Cho H, Kim YK, Lee JS, Park KS, Shin H, Choi I, Lee SH, Park WJ, Park SY, Choi CS, Lin P, Karunasiri M, Tan T, Duann P, Zhu H, Ma J, Ko YG. Mg53-induced irs-1 ubiquitination negatively regulates skeletal myogenesis and insulin signalling. *Nat Commun*. 2013; 4:2354. [PubMed: 23965929]
12. Song R, Peng W, Zhang Y, Lv F, Wu HK, Guo J, Cao Y, Pi Y, Zhang X, Jin L, Zhang M, Jiang P, Liu F, Meng S, Zhang X, Jiang P, Cao CM, Xiao RP. Central role of e3 ubiquitin ligase mg53 in insulin resistance and metabolic disorders. *Nature*. 2013; 494:375–379. [PubMed: 23354051]
13. Young ME, Guthrie PH, Razeghi P, Leighton B, Abbasi S, Patil S, Youker KA, Taegtmeier H. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. *Diabetes*. 2002; 51:2587–2595. [PubMed: 12145175]
14. Haemmerle G, Moustafa T, Woelkart G, Buttner S, Schmidt A, van de Weijer T, Hesselink M, Jaeger D, Kienesberger PC, Zierler K, Schreiber R, Eichmann T, Kolb D, Kotzbeck P, Schweiger M, Kumari M, Eder S, Schoiswohl G, Wongsiriroj N, Pollak NM, Radner FP, Preiss-Landl K, Kolbe T, Rulicke T, Pieske B, Trauner M, Lass A, Zimmermann R, Hoefler G, Cinti S, Kershaw EE, Schrauwen P, Madeo F, Mayer B, Zechner R. Atgl-mediated fat catabolism regulates cardiac mitochondrial function via ppar-alpha and pgc-1. *Nat Med*. 2011; 17:1076–1085. [PubMed: 21857651]
15. Brown MS, Goldstein JL. Selective versus total insulin resistance: A pathogenic paradox. *Cell Metab*. 2008; 7:95–96. [PubMed: 18249166]
16. Lipford JR, Smith GT, Chi Y, Deshaies RJ. A putative stimulatory role for activator turnover in gene expression. *Nature*. 2005; 438:113–116. [PubMed: 16267558]
17. Nawaz Z, Lonard DM, Smith CL, Lev-Lehman E, Tsai SY, Tsai MJ, O'Malley BW. The Angelman syndrome-associated protein, e6-ap, is a coactivator for the nuclear hormone receptor superfamily. *Mol Cell Biol*. 1999; 19:1182–1189. [PubMed: 9891052]
18. Geng F, Wenzel S, Tansey WP. Ubiquitin and proteasomes in transcription. *Annu Rev Biochem*. 2012; 81:177–201. [PubMed: 22404630]
19. van der Horst A, de Vries-Smits AM, Brenkman AB, van Triest MH, van den Broek N, Colland F, Maurice MM, Burgering BM. Foxo4 transcriptional activity is regulated by monoubiquitination and usp7/hausp. *Nat Cell Biol*. 2006; 8:1064–1073. [PubMed: 16964248]
20. Wang X, Xie W, Zhang Y, Lin P, Han L, Han P, Wang Y, Chen Z, Ji G, Zheng M, Weisleder N, Xiao RP, Takeshima H, Ma J, Cheng H. Cardioprotection of ischemia/reperfusion injury by

- cholesterol-dependent mg53-mediated membrane repair. *Circ Res.* 2010; 107:76–83. [PubMed: 20466981]
21. Zhang Y, Lv F, Jin L, Peng W, Song R, Ma J, Cao CM, Xiao RP. Mg53 participates in ischaemic postconditioning through the risk signalling pathway. *Cardiovasc Res.* 2011; 91:108–115. [PubMed: 21285295]
 22. Cao CM, Zhang Y, Weisleder N, Ferrante C, Wang X, Lv F, Zhang Y, Song R, Hwang M, Jin L, Guo J, Peng W, Li G, Nishi M, Takeshima H, Ma J, Xiao RP. Mg53 constitutes a primary determinant of cardiac ischemic preconditioning. *Circulation.* 2010; 121:2565–2574. [PubMed: 20516375]
 23. Liu J, Zhu H, Zheng Y, Xu Z, Li L, Tan T, Park KH, Hou J, Zhang C, Li D, Li R, Liu Z, Weisleder N, Zhu D, Lin P, Ma J. Cardioprotection of recombinant human mg53 protein in a porcine model of ischemia and reperfusion injury. *J Mol Cell Cardiol.* 2014; 80C:10–19. [PubMed: 25533937]
 24. Jia Y, Chen K, Lin P, Lieber G, Nishi M, Yan R, Wang Z, Yao Y, Li Y, Whitson BA, Duann P, Li H, Zhou X, Zhu H, Takeshima H, Hunter JC, McLeod RL, Weisleder N, Zeng C, Ma J. Treatment of acute lung injury by targeting mg53-mediated cell membrane repair. *Nat Commun.* 2014; 5:4387. [PubMed: 25034454]
 25. Weisleder N, Takizawa N, Lin P, Wang X, Cao C, Zhang Y, Tan T, Ferrante C, Zhu H, Chen PJ, Yan R, Sterling M, Zhao X, Hwang M, Takeshima M, Cai C, Cheng H, Takeshima H, Xiao RP, Ma J. Recombinant mg53 protein modulates therapeutic cell membrane repair in treatment of muscular dystrophy. *Sci Transl Med.* 2012; 4:139ra185.