JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 6, 2022

EDITORIAL COMMENT

Cardiac GRK2 and the Communicative Axis Between Heart and Fat*

Bradford G. Hill, PhD

β-adrenergic signaling in the heart has a long and storied past that involves dynamic regulation of G protein-coupled receptor kinase 2 (GRK2), also known as β-adrenergic receptor kinase 1 (βARK1). Classic experiments showed that the multidomain nature of βARK1 provides it with numerous opportunities to interact with different binding partners and to integrate signaling cascades that influence cardiac hypertrophy and function. Interestingly, previous studies in which a short, amino-terminal fragment of βARK1 (βARKnt) was expressed specifically in cardiomyocytes showed that not only does it induce mild cardiac hypertrophy and protect against pressure overload-induced heart failure, but it also diminishes abdominal fat in mice, providing hints of a communicative axis between cardiac βARK1 signaling and whole body metabolism.[1]

In this issue of *JACC: Basic to Translational Science*, Manaserh et al[2] further examined the role of βARK1 in the heart-fat axis, highlighting novel links between cardiac β-adrenergic signaling and systemic metabolism.[2] Mice expressing βARKnt specifically in the heart were provided a high fat diet (HFD) and were shown to gain weight similar to nontransgenic littermate controls. However, the authors observed striking differences in glucose handling: although fasting glucose levels, glucose tolerance, and insulin tolerance were worsened by HFD in control mice, the βARKnt mice were largely protected against diet-induced insulin resistance. Thorough metabolic cage studies demonstrated that βARKnt transgenic mice used carbohydrates more as a metabolic fuel compared with nontransgenic controls, suggesting that expression of βARKnt in the heart affects systemic energy metabolism. Examination of adipose tissue depots revealed that βARKnt transgenic mice had less visceral fat, which was accompanied by remarkable up-regulation of uncoupling protein-1 (UCP-1), providing evidence of heart-initiated conversion of white adipose tissue to a more brown-like (beige) adipose tissue phenotype. Expression of βARKnt in the heart influenced brown adipose tissue depots as well, leading to the development of smaller and more numerous brown adipocytes in transgenic mice fed HFD compared with nontransgenic controls.

Although several questions remain, 1 question is particularly conspicuous. How does the expression of a small fragment of GRK2, specifically in cardiomyocytes, alter the phenotype and function of adipocytes? Although it is clear that follow-up studies will be required to address this question, an important first step is to entertain likely possibilities. One possibility is that the expression of βARKnt in the heart promotes release of endocrine signaling molecule(s) capable of modulating systemic metabolism and adipose tissue phenotype. Although the concept of the heart as an endocrine organ was solidified in the 1970s and 1980s through the discovery of cardiac natriuretic peptides that modulate extracellular fluid volume and blood pressure, it remains unclear how the heart influences the adipose organ. Evidence to date provides a short list of potential candidates, including: mediator complex subunit 13 (MED13)—the cardiac expression of which promotes higher metabolic activity in extracardiac organs such as heart and liver[3]; Krüppel-like factor 5, which influences MED13 levels in the heart, cardiac fibroblast growth factor 21

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the Department of Medicine, Division of Environmental Medicine, Christina Lee Brown Envirome Institute, Diabetes and Obesity Center, University of Louisville, Louisville, Kentucky, USA.

The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2022.02.020

secretion, and adiposity[4]; and cardiac mitsugumin 53, which regulates systemic insulin sensitivity.[5] Whether expression of βARKnt influences these pathways or promotes the release of "cardiokines" that modulate peripheral tissue metabolism and adipose tissue phenotype are exciting hypotheses to test in future studies.

It is also possible that cardiac βARKnt expression influences the metabolic state of the heart, to the extent that it somehow influences extracardiac organ metabolism. Given that the heart is an organ with high metabolic activity and accounts for a significant amount of total body oxygen consumption (~11%), it seems possible that a change in its utilization of substrates (eg, fatty acids or glucose) could affect adipose tissue phenotype and lipid storage. The testing of this possibility appears to require a better understanding of not only how βARKnt impacts cardiac metabolism, but also how changes in cardiac metabolism influence systemic metabolism. Should the βARKnt transgenic hearts promote higher cardiac glucose utilization, this would not only be consistent with the hypertrophic cardiac phenotype, which is typically characterized by higher reliance on glucose for energy, but it may also partly explain the higher levels of carbohydrate utilization found in metabolic cage studies. It might also be possible that βARKnt expression impacts adipose tissue by preventing the adipose "whitening" effect of HFD, which has been associated with down-regulation of electron transport chain components in adipocytes. Nevertheless, this mechanism would not explain the dramatic up-regulation of UCP-1 in visceral adipose tissue in βARKnt mice, which is known to be triggered by peroxisome proliferator activated receptor activation or via circulating hormones such as catecholamines, atrial natriuretic peptide, and bone morphogenic proteins, among others. Although the authors ruled out catecholamines by showing that they were not significantly different between βARKnt and control mice, the other possibilities could be addressed in future studies.

The findings of Manaserh et al[2] also raise a number of additional interesting questions. For example, cardiomyocyte-specific βARKnt expression was shown to modestly increase fibrotic area in the heart with high-fat feeding, despite no difference in fibrosis in mice fed normal chow. This could indicate a paracrine signaling mechanism between cardiac myocytes and fibroblasts that emerges in βARKnt-expressing hearts after weeks of HFD-induced nutrient stress. Previous studies indicate that pressure overload-induced fibrosis is minimized in βARKnt transgenic hearts under normal chow conditions.[1] Thus, it seems that βARKnt expression in cardiomyocytes not only facilitates communication with adipose tissue, but also may influence communication of cardiomyocytes with mesenchymal cells in the heart to influence collagen deposition or turnover. Overall, it is apparent that βARKnt modulates the ability of cardiomyocytes to communicate with other cell types and peripheral organs. It will be interesting to see how our understanding of the heart as an endocrine organ unfolds and to learn how GRK2 may further contribute to the crosstalk between the heart and other tissues.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Hill has received funding from the National Institutes of Health (R01 HL130174, R01 HL147844, P01 HL078825, R01 ES028268, and P30 GM127607).

ADDRESS FOR CORRESPONDENCE: Dr Bradford G. Hill, Department of Medicine, Division of Environmental Medicine, Christina Lee Brown Envirome Institute, Diabetes and Obesity Center, University of Louisville, 580 South Preston Street, Room 321E, Louisville, Kentucky 40202, USA. E-mail: bradford.hill@louisville.edu.

REFERENCES

1. Bledzka KM, Manaserh IH, Grondolsky J, et al. A peptide of the amino-terminus of GRK2 induces hypertrophy and yet elicits cardioprotection after pressure overload. *J Mol Cell Cardiol*. 2021;154:137–153.

2. Manaserh IH, Bledzka KM, Junker A, Grondolsky J, Schumacher SM. A cardiac amino-terminal GRK2 peptide inhibits maladaptive adipocyte hypertrophy and insulin resistance during diet-induced obesity. *J Am Coll Cardiol Basic Trans Science*. 2022;7:563–579.

3. Baskin KK, Grueter CE, Kusminski CM, et al. MED13-dependent signaling from the heart confers leanness by enhancing metabolism in adipose tissue and liver. *EMBO Mol Med*. 2014;6:1610–1621.

4. Pol CJ, Pollak NM, Jurczak MJ, et al. Cardiac myocyte KLF5 regulates body weight via alteration of cardiac FGF21. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865:2125–2137.

5. Wu HK, Zhang Y, Cao CM, et al. Glucose-sensitive myokine/cardiokine MG53 regulates systemic insulin response and metabolic homeostasis. *Circulation*. 2019;139:901–914.

KEY WORDS beiging, cardioprotection, GRK2, metabolism, obesity