Cardiac adaptations to obesity, diabetes and insulin resistance

BBA - Molecular Basis of Disease 1864 (2018) 1905–1907

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Editorial

Cardiac adaptations to obesity, diabetes and insulin resistance☆

Cardiovascular disease remains the leading cause of mortality and morbidity in persons with diabetes. Moreover, the prevalence of heart failure is more than 5-fold higher in diabetes. In the last decades the occurrence of diabetes has increased markedly to become a global epidemic. As a result, there is strong interest in understanding at a molecular level the mechanisms that increase the vulnerability of the heart and vasculature to injury in the context of diabetes. In view of these developments the annual conference of the *Society for Heart and Vascular Metabolism*, held in Beijing (China), October 9–12, 2016 (www.heartmetabolism.org/2016), focused on cardiac adaptations to obesity, diabetes and insulin resistance. The present Special Issue provides state-of-the-art review articles based on the lectures and discussions of various aspects of this topic as presented during the conference. Specifically, these articles highlight the latest information on novel metabolic and signaling mechanisms that contribute to heart failure in diabetes and discuss novel targets and therapies.

Systemic changes associated with diabetes, in particular high plasma glucose concentration (hyperglycemia), dyslipidemia, hormonal alterations such as hyperinsulinemia, and low grade inflammation, have been found to induce structural and functional changes in the cardiomyocyte that trigger the development of so-called “diabetic cardiomyopathy”. Accordingly, the diabetic heart exhibits a range of features that includes oxidative stress, altered substrate metabolism, mitochondrial dysfunction, fibrosis, apoptosis, increased endoplasmic reticulum (ER) stress, impaired autophagy, inflammation, and altered calcium handling. NADPH-oxidases (NOXs), enzymes producing reactive oxygen species (ROS), have been implicated in the increased oxidative stress of the diabetic heart. Synne Hansen and colleagues [1] review our current knowledge regarding the understanding of how NOXs influence cardiac adaptive and maladaptive processes in a diabetic environment, and discuss the suggested application of NOXs as target for diabetes-induced cardiovascular complications.

One of the signaling pathways identified in the heart to be involved in both development, physiological adaptation and pathological changes is that of the MAPK families, particularly p38MAPK. Although diabetic cardiomyopathy has been associated with disrupted p38MAPK signaling, p38MAPK inhibitors have failed in clinical trials due to adverse effects. In their review, Matthieu Ruiz and colleagues [2] discuss the inhibition of MK2, a downstream target of p38MAPK, as an alternative strategy to conclude that MK2 inhibitors are promising as therapy to normalize diabetes-induced changes in cardiac lipid metabolism, calcium handling and contractile dysfunction, while minimizing adverse side effects.

The pancreatic β-cell hormone amylin, which is co-secreted with insulin, has been suggested to play a role in whole-body energy homeostasis. Interestingly, aggregated amylin is found in extra-hepatic tissues including myocardium. Miao Liu and colleagues [3] describe experimental studies that amylin accumulates preferentially in male *versus* female hearts and that its dysregulatory effect on myocyte Ca^{2+} cycling occurs independent of the diabetic remodeling of the heart. These novel data identify circulating aggregated amylin as potential therapeutic target in diabetic cardiomyopathy. In the context of diabetes, the signaling effects of another hormone, *i.e.*, insulin-like growth factor-1, on the cardiovascular system, as reviewed by Wang-Soo Lee and Jaetaek Kim [4], are also of interest.

Desiree Abdurrachim and Jeanine Prompers [5] review the application of ^{31}P magnetic resonance spectroscopy (^{31}P MRS) as a powerful tool to investigate cardiac energetics non-invasively *in vivo* in both man and experimental animals. A specific advantage of this technique is that it allows longitudinal *in vivo* studies of cardiac energetics. One of the currently applied parameters determined with this technique is the ratio of phosphocreatine and adenosine triphosphate (PCr/ATP ratio), which is a useful index of the cardiac energy status. For instance, following a metabolic stress (*e.g.*, exercise, pharmacological intervention), the rate of recovery of the PCr/ATP ratio is a useful estimate of the dynamics of cardiac energy metabolism. With respect to obesity and (type 2) diabetes, the use of ^{31}P MRS has revealed that the PCr/ATP ratio may be an independent predictor of diastolic function.

In search of molecular mechanisms underlying the pathophysiological alterations in the heart in diabetes, Upasna Varma and colleagues [6] review our current understanding of cardiac metabolic dysregulation in diabetes. They also discuss inconsistent findings reported for the role of AMP-activated kinase (AMPK) and β-adrenergic signaling in diabetes. Mechanistic studies depend largely on the availability of appropriate model systems. Cellular models such as cardiomyocytes derived from human stem cells are increasingly being applied. Ilvy Geraets and colleagues [7] describe human embryonic stem cell-derived cardiomyocytes as an *in vitro* model to study cardiac insulin resistance. This model may be used not only for further delineating the underlying mechanism of cardiac insulin resistance but also for evaluating new pharmacological agents and therapeutic strategies.

☆ This article is part of a Special Issue entitled: Cardiac adaptations to obesity, diabetes and insulin resistance, edited by Professors Jan F.C. Glatz, Jason R.B. Dyck and Christine Des Rosiers.

https://doi.org/10.1016/j.bbadis.2018.01.024

Available online 31 January 2018

A relatively new area of intensive research is that of lipid droplets. These organelles have long been considered as being rather inert, but recently have been found to be metabolically active and highly dynamic. The review by Shimeng Xu and collaborators [8] provides state-of-the-art insight into the role of lipid droplets in maintaining lipid homeostasis in both normal circumstances and in human disease. Another relatively new development is the recognition that the protein MG53 participates in the regulation of several metabolic processes, in particular insulin signaling. MG53 is a member of the tripartite motif (TRIM) protein family that is highly expressed in skeletal and cardiac muscle, and is known to contribute to the protective effects of preconditioning on myocardial ischemia/reperfusion injury. Recently, it was found that MG53 can function as an ubiquitin E3 ligase to facilitate proteasome degradation of the insulin receptor thus downregulating insulin signaling. In their review, Xinli Hu and Rui-Ping Xiao [9] provide an overview of the current understanding of the functions of MG53 with focus on its putative role in the pathogenesis of diabetic cardiomyopathy.

Finally, Wang Wang and colleagues [10] give an update on the recent delineation of the role of mitochondria beyond their traditional role as cell powerhouse. Specifically, mitochondria also appear to be dynamic organelles as their size, shape and location ae constantly changing. These morphological changes are designated 'mitochondrial dynamics' and have been found to be part of various cellular signaling mechanisms. Mitochondrial dynamics are controlled by a group of dynamin-related GTPases. The review summarizes the newly identified 'non-canonical' roles of the mitochondrial dynamics proteins, and in particular discusses the roles of fission and fusion in regulating mitochondrial bioenergetics.

Taken together, this special issue presents an updated understanding of the significance of metabolic homeostasis in the cardiovascular system. Myocardial energy metabolism remains a highly dynamic process that is pivotal for securing an optimal contractile function. Detailed insight into the underlying molecular mechanisms is essential for identifying additional diagnostic and therapeutic options to treat aberrations in cardiac functioning seen in the heart in obesity and diabetes.

Transparency document

The Transparency document associated with this article can be found, in the online version.

References

[1] S.S. Hansen, E. Aasum, A.D. Hafstad, The role of NADPH oxidases in diabetic cardiomyopathy, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.07.025.
[2] M. Ruiz, L. Coderre, B.G. Allen, C. Des Rosiers, Protecting the heart through MK2 modulation, toward a role in diabetic cardiomyopathy and lipid metabolism, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.07.015.
[3] M. Liu, A. Hoskins, N. Verma, D.M. Bers, S. Despa, F. Despa, Amylin and diabetic cardiomyopathy - amylin-induced sarcolemmal Ca^{2+} leak is independent of diabetic remodeling of myocardium, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.10.024.
[4] W.S. Lee, J. Kim, Insulin-like growth factor-1 signaling in cardiac aging, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.08.029.
[5] D. Abdurrachim, J.J. Prompers, Evaluation of cardiac energetics by non-invasive ^{31}P magnetic resonance spectroscopy, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.11.013.
[6] U. Varma, P. Koutsifeli, V.L. Benson, K.M. Mellor, L.M.D. Delbridge, Molecular mechanisms of cardiac pathology in diabetes - experimental insights, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.10.035.
[7] I.M.E. Geraets, D. Chanda, F.H.J. Van Tienen, A. Van den Wijngaard, R. Kamps, D. Neumann, Y. Liu, J.F.C. Glatz, J.J.F.P. Luiken, M. Nabben, Human embryonic stem cell-derived cardiomyocytes as an in vitro model to study cardiac insulin resistance, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.12.025.
[8] S. Xu, X. Zhang, P. Liu, Lipid droplet proteins and metabolic diseases, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.07.019.
[9] X. Hu, R.P. Xiao, MG53 and disordered metabolism in striated muscle, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.10.013.
[10] W. Wang, C. Fernandez-Sanz, S.S. Sheu, Regulation of mitochondrial bioenergetics by the non-canonical roles of mitochondrial dynamics proteins in the heart, Biochim. Biophys. Acta (2018), http://dx.doi.org/10.1016/j.bbadis.2017.09.004.

Dr. Jan. F.C. Glatz is Professor of Cardiac Metabolism at the Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, The Netherlands. Currently he serves as chair of the Department of Genetics & Cell Biology as well as deputy-chair of the Department of Clinical Genetics (Maastricht University Medical Center+). In the period 2012–2015 Dr. Glatz was President of the *Society for Heart and Vascular Metabolism* (SHVM). Dr. Glatz's major contributions to understanding cardiac metabolism include the disclosure of the molecular mechanism of cardiac fatty acid uptake, especially the role of membrane substrate transporters (in particular CD36/SR-B2) and that of cytoplasmic heart-type fatty acid-binding protein (FABP3), and the unraveling of the significance of altered cardiac fatty acid handling in obesity-induced cardiac insulin resistance and diabetic cardiomyopathy. His main current scientific interest is the regulation of energy metabolism in the healthy and in the diabetic heart with focus on the application of intracellular membrane substrate transporter recycling for so-called metabolic modulation therapy.

Dr. Jason R. B. Dyck is a Professor in the Department of Pediatrics, a Canada Research Chair in Molecular Medicine, and the Director of the Cardiovascular Research Centre at the University of Alberta. He is also the co-director of the Alberta HEART, which is a program aimed at understanding and treating heart failure. Dr. Dyck has a broad area of research that includes the study of obesity, insulin resistance, diabetic cardiomyopathy, chemotherapy-induced cardiotoxicity, ischemia/reperfusion injury, hypertension and heart failure. These diverse research topics are linked by Dr. Dyck's interest in how alterations in energy metabolism contribute to these conditions.

Dr. Christine Des Rosiers is a Professor in the Department of Nutrition of the *Université de Montréal* and Director of the Montreal Heart Institute Research Centre Metabolomic Laboratory and Platform. She is a founding member of the *Society for Heart and Vascular Metabolism* (SHVM) and is currently serving as President since 2015. The focus of her research is on the role of metabolic alterations in the pathogenesis of disease, particularly heart disease. She has over 25 years of research experience in metabolic investigations using stable isotopes and mass spectrometric-based methodology. She specifically gained recognition for the development of these methods for the metabolic and functional phenotyping of the *ex vivo* working mouse heart. More recently, she has taken the direction of metabolomic initiatives as part of multidisciplinary translational projects aiming at the discovery of biomarkers of disease development or treatment response in various conditions, which include heart disease, but also diabetes, as well as mitochondrial and inflammatory diseases.

Jan F.C. Glatz[a,*], Jason R.B. Dyck[b], Christine Des Rosiers[c]
[a] *Maastricht University, Maastricht, The Netherlands*
[b] *University of Alberta, Edmonton, Alberta, Canada*
[c] *Montréal Heart Institute, Montréal, Canada*
E-mail address: glatz@maastrichtuniversity.nl

* Corresponding author.