ANTIOXIDANTS & REDOX SIGNALING
Volume 15, Number 7, 2011

DOI: 10.1089/ars.2011.3981

Risk Factors in Heart Disease: Therapeutic Interventions

Nilanjana Maulik[1] and Juan A. Sanchez[1,2]

MANY INVESTIGATORS CONTINUE to labor assiduously to elucidate the seemingly endless operant conditions resulting in cardiovascular disease. In aggregate, this work continues to categorize the complex sets of responses of the cardiomyocyte to noxious stimuli. This Forum aims to explore newer concepts and mechanisms contributing to heart tissue injury as well as presenting potential therapeutic strategies by highlighting the work of several laboratories currently engaged in examining nontraditional risk factors and potentially new directions in treatment. In particular, many of the articles presented revolve around two increasingly real threats to heart health from a population perspective: obesity and diabetes. These two conditions present formidable problems not only in the developed world but also globally (20). Addressing these threats requires a deep understanding of the socioeconomic, environmental, and biologic causal factors along with extensive dissemination of data and coordination of investigative activities across all relevant domains.

The current epidemic and projected worldwide increase in obesity-related disorders in the coming decades and, in particular, the concomitant cardiovascular effects of insulin resistance have attracted considerable interest in examining how cardiovascular cells respond and, in some cases, adapt to these conditions (5, 6, 14). The real-world implications of research into myocardial oxidative stress and ischemia/reperfusion under altered fat and glucose metabolism have attracted many investigators toward this area. In particular, the interest in molecules that regulate the catabolism of excess fat and glucose products appears to be a productive if not clinically relevant endeavor. As such, we have attempted to showcase some of these ideas in this Forum.

Yi *et al.* (24), in an original article, describe resistance to the cardioprotective effects of adiponectin in fat-induced diabetes. Adiponectin, a polypeptide hormone that modulates a number of metabolic processes related to fatty acid and glucose regulation, has been shown to have significant myocardial protective effects in nondiabetic animals (7). This hormone, along with other adipokines, has recently received considerable attention, as adipose tissue continues to be increasingly identified as an endocrinologically active organ (11). The predominant transcript in adipocytes, adiponectin, is inversely correlated with the risk of developing cardiovascular disease and diabetes (12, 15, 17). This link is amply reviewed in this Forum by Lau *et al.* (13). These articles further enhance support for the central role played by this hormone in reducing risk for diabetes-related cardiovascular disease.

It is well known that under certain abnormal conditions, including diabetes, elevated levels of advanced glycation endproducts (AGEs) play a dominant role as proinflammatory mediators by the production of reactive oxygen species (19). The pathogenesis of diabetes-related AGE formation within endothelial cells is of increasing interest given that cell's inability to modulate glucose intake resulting in the subsequent development of vasculopathy (4). In another original article in this Forum, Liu *et al.* (16) explore the effects of AGEs on endothelial injury during ischemia/reperfusion and suggest that the increased damage observed results from oxidative stress and subsequent nitrative inactivation of Trx-1. Their research proposes that interventions that can either attenuate signaling or increase Trx-1 activity can potentially mitigate myocardial injury in the diabetic patient.

In keeping with the theme of inflammatory conditions associated with obesity and diabetes, Otani (18) reviews the current understanding of the role of oxidative stress in triggering inflammatory cytokines in adipose tissue, which is increasingly being recognized as a major contributing factor in the vasculopathy and cardiac risk resulting from metabolic syndrome. This syndrome, however, continues to be a source of controversy as it is yet unclear whether the cluster of individual risk factors results in greater total cardiovascular risk than the sum of its parts (10). Nonetheless, despite doubt regarding its value as a unique risk marker, the condition appears to be a target-rich source for investigations into the inflammatory occurring at the crossroads of obesity and insulin resistance.

The critical role of Toll-like receptors in myocardial inflammation is discussed in individual articles by investigators from distinct laboratories (2, 8). Ha *et al.* (8), for example, review the relationship between these receptors and other intracellular signaling pathways during ischemia/reperfusion. In addition, they discuss the role they play in the generation of important innate inflammatory responses by cardiac myocytes, including the generation of cytokines and chemokines. This review is complemented by that of Avlas *et al.* (2), which outlines how these receptors on cardiac cells react to immunological triggers supporting their central role in various disease states, including the cardiac depression seen during sepsis.

[1]Molecular Cardiology and Angiogenesis Laboratory, Department of Surgery, University of Connecticut School of Medicine, Farmington, Connecticut.
[2]Department of Surgery, Saint Mary's Hospital, Waterbury, Connecticut.

The original article by Adluri *et al.* (1) documented that disruption of hypoxia-inducible factor-prolyl hydroxylase-1 leads to cardioprotection by stabilization of hypoxia-inducible factor-1α followed by increased mRNA expression of proangiogenic and antiapoptotic molecules in the ischemic/reperfused myocardium. Again, the cardioprotective effects of Heme oxygenase-1 (HO-1), a stress response protein that provides antioxidant and anti-inflammatory activity, are extensively surveyed by Wu *et al.* (23). The article examines HO-1 from a variety of different perspectives, including the development of atherosclerosis, plaque stability, arterial injury, and repair, along with other clinically relevant conditions, including diabetes and angiogenesis. HO-1, a member of the HO family, appears to be an important component in the body's protection against oxidative stress. Its ubiquity and pivotal role in cardiovascular homeostasis makes its modes of action an important object of study with potential implications in the treatment of disease.

Elevated levels of homocystein in plasma have long been known to result in an increased risk for cardiovascular disease. In a review by Steed and Tyagi (21), the mechanisms of cardiovascular remodeling in hyperhomocysteinemia are described. They report on studies in their laboratory and others describing the complex nature of increased oxidative/nitrative oxidation of matrix metalloproteinase activity resulting in loss of elastic compliance and the significant vascular remodeling often found in this condition.

Two additional articles explore the potential therapeutic application of stem cells in myocardial repair. Han and Yoon (9) review current techniques for generating pluripotent stem cells resulting from reprogrammed somatic cells as well as their enormous potential in the field of regenerative medicine and other therapeutic applications. Additionally, Zuba-Surma and colleagues (25) examine the characteristics and potential use of very small embryonic stem cells that are capable of producing cellular derivatives from all three germ layers, including their ability to differentiate into various cardiovascular cells and to secrete several cardioprotective factors.

Alterations in the function of the ryanodine receptor, the major cellular mediator of calcium-induced calcium release, can result in critical dysregulation of physiologic processes with profound clinical manifestations, including atrial and ventricular arrhythmias (26). Turan and Vassort (22) review the impact of diabetes on the capacity of this receptor to regulate calcium transport in the myocardium. The article provides an excellent summary of recent findings regarding the redox regulation of calcium transport systems in the heart both in health and disease.

Finally, the contribution of ionizing radiation to cardiovascular disease is explored by Baker and his colleagues (3), who present evidence of this association even at low levels of exposure. Not often included on the list of cardiovascular risk factors, the prevalence of radiation, both as a result of background exposure as well as that incurred through the healthcare system, should be of considerable concern. Biomedical research into the underlying mechanisms of radiation-induced cardiac injury and repair should be a focus of increased inquiry—particularly, in light of potentially new sources of threats such as worldwide terrorism and exposure to cosmic radiation during long-duration spaceflight.

It is hoped that this Forum generates substantial interest in these novel concepts and that promising new technologies emerge as a result. The increasingly obvious complexity in the biology of cardiovascular responses to injury and the many causative conditions involved creates a compelling reason to periodically review and disseminate fresh ideas such as these in the hope that other investigators can increasingly contribute to an enhanced mechanistic understanding and thereby generating innovative solutions in the future.

References

1. Adluri RS, Thirunavukkarasu M, Dunna NR, Zhan L, Oriowo B, Takeda K, Sanchez JA, Otani H, Maulik G, Fong GH, and Maulik N. Disruption of hypoxia-inducible transcription factor-prolyl hydroxylase domain-1 (PHD-1$^{-/-}$) attenuates *ex vivo* myocardial ischemia/reperfusion injury through hypoxia-inducible factor-1α transcription factor and its target genes in mice. *Antioxid Redox Signal* 15: 1789–1797, 2011.
2. Avlas O, Fallach R, Shainberg A, Porat E, and Hochhauser E. Toll-like receptor 4 stimulation initiates an inflammatory response that decreases cardiomyocyte contractility. *Antioxid Redox Signal* 15: 1895–1909, 2011.
3. Baker JE, Moulder JE, and Hopewell JW. Radiation as a risk factor for cardiovascular disease. *Antioxid Redox Signal* 15: 1945–1956, 2011.
4. Brownlee M. The pathobiology of diabetic complications. *Diabetes* 54: 1615–1625, 2005.
5. Farag YMK and Gaballa MR. Diabesity: an overview of a rising epidemic. *Nephrol Dialysis Transpl* 26: 28–35, 2011.
6. Gersh BJ, Sliwa K, Mayosi BM, and Yusuf S. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. *Eur Heart J* 31: 642–648, 2010.
7. Goldstein BJ, Scalia RG, and Ma XL. Protective vascular and myocardial effects of adiponectin. *Nat Clin Pract Cardiovasc Med* 6: 27–35, 2008.
8. Ha T, Liu L, Kelley J, Kao R, Williams D, and Li C. Toll-like receptors: new players in myocardial ischemia/reperfusion injury. *Antioxid Redox Signal* 15: 1875–1893, 2011.
9. Han JW and Yoon Ys. Induced pluripotent stem cells: emerging techniques for nuclear reprogramming. *Antioxid Redox Signal* 15: 1799–1820, 2011.
10. Kahn R, Buse J, Ferrannini E, and Stern M. The metabolic syndrome: time for a critical appraisal. *Diabetes Care* 28: 2289–2304, 2005.
11. Kang K. White adipose tissue as an endocrine organ. In: *Autologous Fat Transfer*, edited by Shiffman MA. Springer, 2010, pp. 37–40.
12. Karastergiou K, Mohamed-Ali V, Jahangiri M, and Kaski JC. Review: adiponectin for prediction of cardiovascular risk? *Br J Diabetes Vasc Dis* 9: 150, 2009.
13. Lau WB, Tao L, Wang Y, Li R, and Ma XL. Systemic adiponectin malfunction as a risk factor for cardiovascular disease. *Antioxid Redox Signal* 15: 1863–1873, 2011.
14. Levenson JW, Skerrett PJ, and Gaziano JM. Reducing the global burden of cardiovascular disease: the role of risk factors. *Prev Cardiol* 5: 188–199, 2002.
15. Li S, Shin HJ, Ding EL, and van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 302: 179–188, 2009.
16. Liu Y, Ma Y, Wang R, Xia C, Zhang R, Lian K, Luan R, Sun L, Yang L, Lau WB, Wang H, and Tao L. Advanced glycation end products accelerate ischemia/reperfusion injury through receptor of advanced end product/nitrative thior-

edoxin inactivation in cardiac microvascular endothelial cells. *Antioxid Redox Signal* 15: 1769–1778, 2011.
17. Maiolino G, Cesari M, Sticchi D, Zanchetta M, Pedon L, Antezza K, Pessina AC, and Rossi GP. Plasma adiponectin for prediction of cardiovascular events and mortality in high-risk patients. *J Clin Endocrinol Metab* 93: 3333–3340, 2008.
18. Otani H. Oxidative stress as pathogenesis of cardiovascular risk associated with metabolic syndrome. *Antioxid Redox Signal* 15: 1911–1926, 2011.
19. Rojas A, Mercadal E, Figueroa H, and Morales MA. Advanced glycation and ROS: a link between diabetes and heart failure. *Curr Vasc Pharmacol* 6: 44–51, 2008.
20. Seidell JC. Dietary fat and obesity: an epidemiologic perspective. *Am J Clin Nutr* 67(3 Suppl): 546S–550S, 1998.
21. Steed MM and Tyagi SC. Mechanisms of cardiovascular remodeling in hyperhomocysteinemia. *Antioxid Redox Signal* 15: 1927–1943, 2011.
22. Turan B and Vassort G. Ryanodine receptor: a new therapeutic target to control diabetic cardiomyopathy. *Antioxid Redox Signal* 15: 1847–1861, 2011.
23. Wu ML, Ho YC, and Yet SF. A central role of heme oxygenase-1 in cardiovascular protection. *Antioxid Redox Signal* 15: 1835–1846, 2011.
24. Yi W, Sun Y, Gao E, Wei X, Lau WB, Zheng Q, Wang Y, Yuan Y, Wang X, Tao L, Li R, Koch W, and Ma XL. Reduced cardioprotective action of adiponectin in high-fat diet–induced type II diabetic mice and its underlying mechanisms. *Antioxid Redox Signal* 15: 1779–1788, 2011.
25. Zuba-Surma EK, Wojakowski W, Ratajczak MZ, and Dawn B. Very small embryonic-like stem cells: biology and therapeutic potential for heart repair. *Antioxid Redox Signal* 15: 1821–1834, 2011.
26. Zucchi R and Ronca-Testoni S. The sarcoplasmic reticulum Ca2+ channel/ryanodine receptor: modulation by endogenous effectors, drugs and disease states. *Pharmacol Rev* 49: 1–51, 1997.

Address correspondence to:
Dr. Nilanjana Maulik
Molecular Cardiology and Angiogenesis Laboratory
Department of Surgery
University of Connecticut School of Medicine
263 Farmington Ave.
Farmington, CT 06032-1110

E-mail: nmaulik@neuron.uchc.edu

Date of first submission to ARS Central, March 8, 2011; date of acceptance, March 13, 2011.

Abbreviations Used

AGEs = advanced glycation end-products
HO-1 = Heme oxygenase-1

This article has been cited by: