Acquired and innate cardioprotection

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WITH AGING OF THE POPULATION, cardiovascular disease is the leading cause of death, disability, and morbidity across continents. In a series of mini-reviews, the Journal of Applied Physiology highlights the most recent advances in molecular and integrative physiology that have provided new insights in understanding the pathobiology of cardiovascular disease, establishing platforms for novel strategies of care, including disease risk prediction and prevention. Despite current aggressive approaches in patient management, including reperfusion therapy in the context of acute coronary syndrome, a limiting factor in averting poor outcome is the inherent susceptibility of the myocardium to ischemic insult and lethal cell injury (3). Therefore the concept of cardioprotection has emerged as an important new direction aimed at protecting cardiac cells under stress. Collectively, the confluence of genomics, proteomics, metabolomics, molecular imaging, and applied systems biology has enabled the resolution of the transcriptome and the downstream signaling pathways, effectors, and mediators central to innate or acquired myocardial protection, which are corrupted in aging or with disease (4, 6).

In particular, the dissection of intimate processes fundamental to endogenous protective mechanisms has revealed that the heart cannot simply be viewed as a collateral casualty of an environmental challenge. Rather the myocardium senses and responds to stress, actively adapting its phenotype to secure self-preservation. Mapping the nucleocytoplasmic circuits of the stress response has led to the identification of biosensors and metabolic pathways responsible for decoding and transducing signals of distress, triggering a systems-level homeostatic reaction (5). This previously unrecognized myocardial plasticity underscores the paradigm of preventive therapy or “vaccination” against the sequelae of ischemia-reperfusion injury (2). Exposure to episodes of mild ischemia precondition the myocardium, reducing the impact of subsequent prolonged insult. Ischemic preconditioning underlies the “warm-up” phenomenon first described by Heberden in the 18th Century. Severe angina during initial effort decreases in intensity with subsequent exercise, a phenomenon also observed in serial exercise testing. In fact, in certain patients, the presence of angina before myocardial infarction has been associated with reduced infarct size, preservation of ventricular function, and lower in-hospital mortality rates. Dissection of disease processes thus offers an unprecedented opportunity to identify and intervene in the earliest preclinical stages of disease, prior to irreversible disruption of tissue and decompensation of organ function (7).

Advances in the new biology have opened a window on the molecular ontogeny of heart disease syndromes, defining the spatiotemporal sequence of genetic and molecular alterations integrated at the systems level to form the mechanistic foundation from risk burden to development of overt disease. New emphasis placed on systems-based genomic approaches aims to stratify individual risk for coronary artery disease and achieve targeted interventions for enhanced myocardial tolerance to injury. As pathways of endogenous cardioprotection are increasingly deciphered, population-based validation of disease susceptibility has created the prospect for implementation of the principles of personalized medicine. The sciences of molecular medicine have indeed provided a powerful catalyst to generate integrated diagnostic and therapeutic paradigms tailored to the genetic and molecular profile of the individual patient to enhance specificity of care, reduce therapeutic variability, and minimize adverse drug effects.

Concomitantly, the emergence of stem cell technology provides a unique opportunity for myocardial regeneration (1). Cell-based clinical trials use adult stem cell approaches to repair damage sustained following acute myocardial infarction or restore pump function in congestive heart failure. While improvement in ejection fraction has been demonstrated, discrepancies in outcome raise the issue of cellular competence and intertrial variability. It remains uncertain whether implanted somatic stem cells reliably contribute to regeneration, whether the benefit of cellular therapy is derived from contribution to myocardial contractility, or whether implanted cells create an environment promoting self-repair. A limiting factor to establishing the benefit of a stem cell-based approach is the lack of appreciation of the most efficacious cell and the specific underlying repair mechanism. With validation of cellular phenotypes and optimizing performance, the next generation of clinical trials should achieve increasing intertrial consistency translating a novel cardioprotective modality from the bench to the bedside (1).

The promise that lies ahead is in the translation of fundamental principles of stress adaptation, probed in the experimental setting and tested in discrete patient cohorts, into
broader diagnostic approaches and targeted therapeutic modalities applied to disease entities in the population at large. The ultimate goal is to implement a clinically validated algorithm that maps stress tolerance in both health and disease for evidence-based decision making in patient management. Establishing comprehensive genetic profiles of stress-response pathways is a critical step in the implementation of molecular screens to identify subjects at risk for disease due to deficient cardioprotection. Molecular diagnostic batteries will facilitate determination of differential diagnosis, prognosis, and selection of adequate therapy to restore adaptation to stress (8). The ability for individualized detection of stress intolerance and targeted repair of deficits in the adaptive response provides a real opportunity for the further advancement of cardiovascular medicine in the decade ahead.

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REFERENCES