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2010 Riley Heart Center Symposium on Cardiac Development: Cardiomyocyte Injury and Protection

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Heart failure, a common event in childhood with significant morbidity and mortality, has an impact on both children and adults. In adult medicine, heart failure is largely related to coronary insufficiency acquired over years. In children, the blood supply to the heart is rarely compromised, and the nutrient and oxygen supplies are good. The etiologies of heart failure in childhood are thus strikingly different from those for adults and can result from congenital structural defects, inherited cardiomyopathies, acquired disease (e.g., infection or exposure to cardiotoxic agents), or ischemia-reperfusion injury during open heart surgery performed to repair structural defects (Fig. 1).

Congenital heart defects, the leading cause of heart failure among children, result from abnormal heart morphogenesis. Children most commonly present for diagnosis between birth and the age of 1 year. Moreover, congenital heart defects are found in approximately 1% of all newborns, making this the most common birth defect in humans [5]. Dilated or hypertrophic cardiomyopathies remain the principal indication for cardiac transplantation among children and are most common in children older than 1 year [1].

Compared with children who have congenital heart defects, children with dilated cardiomyopathy typically are older and well grown at presentation. The prognosis of dilated cardiomyopathy in children is poor, with a survival rate of only 60% at 5 years [3].

Dilated or hypertrophic cardiomyopathies in children are associated with cardiomyocyte death [2, 13]. Inherited cardiomyopathies (i.e., abnormalities of sarcomeric or cytoskeletal proteins) constitute an important class of dilated or hypertrophic cardiomyopathies in children [7, 11]. Acquired injuries also are a major source of dilated cardiomyopathies in children, resulting from surgical interventions with both acute and chronic adverse effects on cardiomyocyte viability and function [6, 12], infection such as viral myocarditis [8], and medication such as anthracycline chemotherapy for cancer [9, 14].

Despite the importance of heart failure in children and infants, it has been less well studied than heart failure in adults, for which a basic understanding and a rich literature exist. As a result, therapy for children with heart failure has advanced more slowly. To advance our ability to treat heart failure in children, it is of critical importance to develop an understanding of the cellular and molecular mechanisms underlying the genesis of congenital heart defects and to develop an understanding of signal transduction pathways

that have a negative impact on cardiomyocyte function and survival during the progression of childhood heart failure.

To help advance the overall field of cardiovascular development through the sharing of information and the facilitation of collaborative investigations between physicians and scientists, the Riley Heart Center Symposium on Cardiac Development was first organized on 2008. That inaugural symposium focused with its title on The Growth and Morphogenesis of the Ventricular Wall and had a subfocus on the etiology of ventricular noncompaction [4]. The second symposium in 2009, entitled Transcriptional Unification of Heart Morphogenesis, focused on key transcriptional and signaling cascades essential for normal cardiogenesis [10].

The third symposium was held 12–14 September 2010, at Riley Hospital for Children, Indiana University School of Medicine (IUSM). The symposium, entitled Cardiomyocyte Injury and Protection, focused on key cellular and molecular events involved in cardiomyocyte death induced by acquired injuries, genetic defects, or both. The symposium aimed to provide a better understanding of the biochemical basis of different forms of cell death, the significance of these processes in the pathogenesis of heart failure, and how to translate these fundamental discoveries into clinical settings.

The participants in the symposium were selected to encompass the basic, clinical, and translational aspects of the focused area. The symposium featured 18 national or international recognized clinical and basic scientists from the United States and Canada. In attendance were faculty, postdoctoral fellows, clinical fellows, graduate students, and staff from the Riley Heart Research Center, as well as returning speakers of previous symposiums and other guests invited by the meeting organizers from the Herman B Wells Center, the basic science departments at IUSM, the Krannert Institute of Cardiology. Other special guests also attended this symposium.

The symposium consisted of three sessions entitled (1) Mechanisms of Cardiomyocyte Death: Apoptosis, Autophagy, and Necrosis, (2) Signaling Pathways Regulating Cardiomyocyte Survival and Death, and (3) Cardiac Protection and Treatment.

Session 1 focused on the molecular mechanisms that mediate three major forms of actively regulated cardiomyocyte death in the heart, such as apoptosis, autophagy, and necrosis, and on their contribution to the pathogenesis of heart failure. The speakers used diverse animal models and approaches to detect and quantify each form of cell death in vitro and in vivo, dissect their regulatory mechanisms and interrelationships, and highlight their functional importance in pathological remodeling

Session 2 focused on several signaling pathways that mediate or antagonize noxious stimuli originated from inside or outside of cell, triggering cell death. The speakers discussed the roles and mechanisms of protein kinases, phosphatases, microRNAs, transcriptional factors, and membrane microdomains regulating cardiomyocyte death and survival.

Session 3 focused on the etiology and characterization of human heart failure as well as strategies for prevention and treatment of these genetic or acquired diseases. The session featured presentation concerning anthracycline-associated cardiotoxicity among long-term survivors of childhood cancer, arrhythmogenic right ventricular dysplasia, mitochondrial cardiomyopathies, and ischemia-reperfusion injury. The speakers also discussed the use of cardiac tissue engineering, mechanical support, and transactivator of transcription-mediated protein replacement strategies for therapeutic interventions used to treat pediatric cardiac patients.

This special issue of *Pediatric Cardiology* contains a compilation of articles reviewing the subjects discussed at the 2010 Riley Heart Symposium. The articles provide a state-of-the-art review of basic and clinical studies focused on the evaluation and regulation of cardiomyocyte survival in the pathogenesis of heart failure, as well as their potential implication in the development of new therapeutic approaches aimed at improving current clinical practice for the treatment of heart failure. The overall goal of the meeting was to foster collaborative projects between clinical and basic scientists dedicated to improving the diagnosis, treatment, and prevention of heart failure in the young. The articles reported in this special issue of *Pediatric Cardiology* have the same aim.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Origins of childhood heart failure