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HIGHLIGHTS OF THE YEAR

Editor-in-Chief's Top Picks From 2017

Valentin Fuster

Each week, I record audio summaries for every article in *JACC*, as well as an issue summary. While this process has been time-consuming, I have become quite familiar with every paper that we publish. Thus, I personally select papers (both original investigations and review articles) from 15 distinct specialties each year for your review. In addition to my personal choices, I have included manuscripts that have been the most accessed or downloaded on our websites, as well as those selected by the *JACC* Editorial Board members. In order to present the full breadth of this important research in a consumable fashion, we will present these manuscripts in this issue of *JACC*.

The highlights comprise the following sections: Basic & Translational Research, Cardiac Failure, Cardiomyopathies/Myocardial & Pericardial Diseases, Cardio-oncology, Congenital Heart Disease, Coronary Disease & Interventions, CVD Prevention & Health Promotion, Hypertension, Imaging, Metabolic & Lipid Disorders, Rhythm Disorders, Valvular Heart Disease, and Vascular Medicine (1–110).

BASIC & TRANSLATIONAL RESEARCH

The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels

F. Paneni, et al.

Cardiovascular disease (CVD) presents a great burden for elderly patients, their caregivers, and health systems. Structural and functional alterations of vessels accumulate throughout life, culminating in increased risk of developing CVD. The growing elderly population worldwide highlights the need to understand how aging promotes CVD in order to develop new strategies to confront this challenge. This review provides examples of some major unresolved clinical problems encountered in daily cardiovascular practice as we care for elderly patients. Next, the authors summarize the current understanding of the mechanisms implicated in cardiovascular aging, and the potential for targeting novel pathways implicated in endothelial dysfunction, mitochondrial oxidative stress, chromatin remodeling, and genomic instability. Lastly, the authors consider critical aspects of vascular repair, including autologous transplantation of bone marrow-derived stem cells in elderly patients (1).

Basic Biology of Oxidative Stress and the Cardiovascular System: Part 1 of a 3-Part Series

M.N. Sack, et al.

The generation of reactive oxygen species (ROS) is a fundamental aspect of normal human biology. However, when ROS generation exceeds endogenous antioxidant capacity, oxidative stress arises. If unchecked, ROS production and oxidative stress mediate tissue and cell damage that can spiral in a cycle of inflammation and more oxidative stress. This article is part 1 of a 3-part series covering the role of oxidative stress in cardiovascular disease. The broad theme of this first paper is the mechanisms and biology of oxidative stress. Specifically, the authors review the basic biology of oxidative stress, relevant aspects of mitochondrial function, and stress-related cell death pathways (apoptosis and necrosis) as they relate to the heart and cardiovascular system. They then explore telomere biology and cell senescence. As important regulators and sensors of oxidative stress, telomeres are segments of repetitive nucleotide sequence at each end of a chromosome that protect the chromosome ends from deterioration (2).

A Combination of Allogeneic Stem Cells Promotes Cardiac Regeneration

M. Natsumeda, et al.

BACKGROUND The combination of autologous mesenchymal stem cells (MSCs) and cardiac stem cells (CSCs) synergistically reduces scar size and improves cardiac function in ischemic cardiomyopathy. Whereas allogeneic (allo-)MSCs are immunoevasive, the capacity of CSCs to similarly elude the immune system remains controversial, potentially limiting the

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success of allogeneic cell combination therapy (ACCT).

OBJECTIVES This study sought to test the hypothesis that ACCT synergistically promotes cardiac regeneration without provoking immunologic reactions.

METHODS Göttingen swine with experimental ischemic cardiomyopathy were randomized to receive transendocardial injections of allo-MSCs + allo-CSCs (ACCT: 200 million MSCs/1 million CSCs, n = 7), 200 million allo-MSCs (n = 8), 1 million allo-CSCs (n = 4), or placebo (Plasma-Lyte A, n = 6). Swine were assessed by cardiac magnetic resonance imaging and pressure volume catheterization. Immune response was tested by histologic analyses.

RESULTS Both ACCT and allo-MSCs reduced scar size by −11.1 ± 4.8% (p = 0.012) and −9.5 ± 4.8% (p = 0.047), respectively. Only ACCT, but not MSCs or CSCs, prevented ongoing negative remodeling by offsetting increases in chamber volumes. Importantly, ACCT exerted the greatest effect on systolic function, improving the end-systolic pressure-volume relation (+0.98 ± 0.41 mm Hg/ml; p = 0.016). The ACCT group had more phosphohistone H3+ (a marker of mitosis) cardiomyocytes (p = 0.04), and noncardiomyocytes (p = 0.0002) than did the placebo group in some regions of the heart. Inflammatory sites in ACCT and MSC-treated swine contained immunotolerant $CD3^+/CD25^+/FoxP3^+$ regulatory T cells (p < 0.0001). Histologic analysis showed absent to low-grade inflammatory infiltrates without cardiomyocyte necrosis.

CONCLUSIONS ACCT demonstrates synergistic effects to enhance cardiac regeneration and left ventricular functional recovery in a swine model of chronic ischemic cardiomyopathy without adverse immunologic reaction. Clinical translation to humans is warranted (3).

Impact of Oxidative Stress on the Heart and Vasculature: Part 2 of a 3-Part Series

T. Münzel, et al.

Vascular disease and heart failure impart an enormous burden in terms of global morbidity and mortality. Although there are many different causes of cardiac and vascular disease, most causes share an important pathological mechanism: oxidative stress. In the failing heart, oxidative stress occurs in the myocardium and correlates with left ventricular dysfunction. Reactive oxygen species (ROS) negatively affect myocardial calcium handling, cause arrhythmia, and contribute to cardiac remodeling by inducing hypertrophic signaling, apoptosis, and necrosis. Similarly, oxidative balance in the vasculature is tightly regulated by a wealth of pro- and antioxidant systems that orchestrate region-specific ROS production and removal. Reactive oxygen species also regulate multiple vascular cell functions, including endothelial and smooth muscle cell growth, proliferation, and migration; angiogenesis; apoptosis; vascular tone; host defenses; and genomic stability. However, excessive levels of ROS promote vascular disease through direct and irreversible oxidative damage to macromolecules, as well as disruption of redox-dependent vascular wall signaling processes (4).

Interleukin-1 Beta as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS and Beyond

P. Libby

Inflammatory pathways drive atherogenesis and link conventional risk factors to atherosclerosis and its complications. One inflammatory mediator has come to the fore as a therapeutic target in cardiovascular disease. The experimental and clinical evidence reviewed here support interleukin-1 beta (IL-1β) as both a local vascular and systemic contributor in this regard. Intrinsic vascular wall cells and lesional leukocytes alike can produce this cytokine. Local stimuli in the plaque favor the generation of active IL-1β through the action of a molecular assembly known as the inflammasome. Clinically applicable interventions that interfere with IL-1 action can improve cardiovascular outcomes, ushering in a new era of anti-inflammatory therapies for atherosclerosis. The translational path described here illustrates how advances in basic vascular biology may transform therapy. Biomarker-directed application of anti-inflammatory interventions promises to help us achieve a more precise and personalized allocation of therapy for our cardiovascular patients (5).

LOX-1 in Atherosclerosis and Myocardial Ischemia: Biology, Genetics, and Modulation

N.V.K. Pothineni, et al.

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), one of the scavenger receptors for oxidized low-density lipoprotein cholesterol (ox-LDL), plays a crucial role in the uptake of ox-LDL by cells in the arterial wall. Mounting evidence suggests a role for LOX-1 in various steps of the atherosclerotic process, from initiation to plaque destabilization. Studies of