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HIGHLIGHTS OF THE YEAR

Editor-in-Chief's Top Picks From 2016: Part One

Valentin Fuster, MD, PhD

Each week, I record audio summaries for every article in *JACC*, as well as an issue summary. While this process has been incredibly 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*.

Part One includes the sections: Basic & Translational Research, Cardiac Failure, Cardiomyopathies/Myocardial & Pericardial Diseases, Congenital Heart Disease, Coronary Disease & Interventions, and CVD Prevention & Health Promotion (1–74).

Part Two will include the sections: CV Medicine & Society, Hypertension, Imaging, Metabolic & Lipid Disorders, Rhythm Disorders, Valvular Heart Disease, and Vascular Medicine.

BASIC & TRANSLATIONAL RESEARCH

Aβ Amyloid Pathology Affects the Hearts of Patients With Alzheimer's Disease: Mind the Heart

L. Troncone, et al.

BACKGROUND Individually, heart failure (HF) and Alzheimer's disease (AD) are severe threats to population health, and their potential coexistence is an alarming prospect. In addition to sharing analogous epidemiological and genetic profiles, biochemical characteristics, and common triggers, the authors recently recognized common molecular and pathological features between the 2 conditions. Whereas cognitive impairment has been linked to HF through perfusion defects, angiopathy, and inflammation, whether patients with AD present with myocardial dysfunction, and if the 2 conditions bear a common pathogenesis as neglected siblings are unknown.

OBJECTIVES Here, the authors investigated whether amyloid beta (Aβ) protein aggregates are present in the hearts of patients with a primary diagnosis of AD, affecting myocardial function.

METHODS The authors examined myocardial function in a retrospective cross-sectional study from a cohort of AD patients and age-matched controls. Imaging and proteomics approaches were used to identify and quantify Aβ deposits in AD heart and brain specimens compared with controls. Cell shortening and calcium transients were measured on isolated adult cardiomyocytes.

RESULTS Echocardiographic measurements of myocardial function suggest that patients with AD present with an anticipated diastolic dysfunction. As in the brain, $A\beta_{40}$ and $A\beta_{42}$ are present in the heart, and their expression is increased in AD.

CONCLUSIONS Here, the authors provide the first report of the presence of compromised myocardial function and intramyocardial deposits of Aβ in AD patients. The findings depict a novel biological framework in which AD may be viewed either as a systemic disease or as a metastatic disorder leading to heart, and possibly multiorgan failure. AD and HF are both debilitating and life-threatening conditions, affecting enormous patient populations. Our findings underline a previously dismissed problem of a magnitude that will require new diagnostic approaches and treatments for brain and heart disease, and their combination (1).

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy

R.H. Falk, et al.

The amyloidoses are a group of protein-folding disorders in which ≥1 organ is infiltrated by proteinaceous deposits known as amyloid. The deposits are derived from 1 of several amyloidogenic precursor proteins, and the prognosis of the disease is determined both by the organ(s) involved and the type of amyloid. Amyloid involvement of the heart (cardiac amyloidosis) carries the worst prognosis of any involved organ, and light-chain (AL) amyloidosis is the most serious form of the disease. The last decade has seen considerable progress in understanding the amyloidoses. In this review, current and novel approaches to the diagnosis and treatment of cardiac amyloidosis are discussed, with particular reference to AL amyloidosis in the heart (2).

Genetic and Pharmacological Inhibition of TREM-1 Limits the Development of Experimental Atherosclerosis

J. Joffre, et al.

BACKGROUND Innate immune responses activated through myeloid cells contribute to the initiation, progression, and complications of atherosclerosis in experimental models. However, the critical upstream pathways that link innate immune activation to foam cell formation are still poorly identified.

OBJECTIVES This study sought to investigate the hypothesis that activation of the triggering receptor expressed on myeloid cells (TREM-1) plays a determinant role in macrophage atherogenic responses.

METHODS After genetically invalidating *Trem-1* in chimeric $Ldlr^{-/-}$ $Trem\text{-}1^{-/-}$ mice and double knockout $ApoE^{-/-}$ $Trem\text{-}1^{-/-}$ mice, we pharmacologically inhibited Trem-1 using LR12 peptide.

RESULTS $Ldlr^{-/-}$ mice reconstituted with bone marrow deficient for *Trem-1* ($Trem\text{-}1^{-/-}$) showed a strong reduction of atherosclerotic plaque size in both the aortic sinus and the thoracoabdominal aorta, and were less inflammatory compared to plaques of $Trem\text{-}1^{+/+}$ chimeric mice. Genetic invalidation of *Trem-1* led to alteration of monocyte recruitment into atherosclerotic lesions and inhibited toll-like receptor 4 (TLR 4)-initiated proinflammatory macrophage responses. We identified a critical role for Trem-1 in the upregulation of cluster of differentiation 36 (CD36), thereby promoting the formation of inflammatory foam cells. Genetic invalidation of Trem-1 in $ApoE^{-/-}/Trem\text{-}1^{-/-}$ mice or pharmacological blockade of Trem-1 in $ApoE^{-/-}$ mice using LR-12 peptide also significantly reduced the development of atherosclerosis throughout the vascular tree, and lessened plaque inflammation. TREM-1 was expressed in human atherosclerotic lesions, mainly in lipid-rich areas with significantly higher levels of expression in atheromatous than in fibrous plaques.

CONCLUSIONS We identified TREM-1 as a major upstream proatherogenic receptor. We propose that TREM-1 activation orchestrates monocyte/macrophage proinflammatory responses and foam cell formation through coordinated and combined activation of CD36 and TLR4. Blockade of TREM-1 signaling may constitute an attractive novel and double-hit approach for the treatment of atherosclerosis (3).

Genetics and Genomics of Single-Gene Cardiovascular Diseases: Common Hereditary Cardiomyopathies as Prototypes of Single-Gene Disorders

A.J. Marian, et al.

This is the first of 2 review papers on genetics and genomics appearing as part of the series on "omics." Genomics pertains to all components of an organism's genes, whereas genetics involves analysis of a specific gene or genes in the context of heredity. The paper provides introductory comments, describes the basis of human genetic diversity, and addresses the phenotypic consequences of genetic variants. Rare variants with large effect sizes are responsible for single-gene disorders, whereas complex polygenic diseases are typically due to multiple genetic variants, each exerting a modest effect size. To illustrate the clinical implications of genetic variants with large effect sizes, 3 common forms of hereditary cardiomyopathies are discussed as prototypic examples of single-gene disorders, including their genetics, clinical manifestations, pathogenesis, and treatment. The genetic basis of complex traits is discussed in a separate paper (4).

Genetics: Implications for Prevention and Management of Coronary Artery Disease

T.L. Assimes, et al.

An exciting new era has dawned for the prevention and management of coronary artery disease (CAD) utilizing genetic risk variants. The recent identification of over 60 susceptibility loci for CAD confirms not only the importance of established risk factors, but also the