Ranolazine Decreases Mechanosensitivity of the Voltage-Gated Sodium Ion Channel Na\textsubscript{v}1.5: A Novel Mechanism of Drug Action

The voltage-gated sodium-selective ion channel Na\textsubscript{v}1.5 is densely expressed in the myocardium and is responsible for the inward current during phase 0 of the action potential. Na\textsubscript{v}1.5 is also expressed in the gastrointestinal tract. Na\textsubscript{v}1.5 is mechanosensitive, with acute stretch being generally excitatory to this channel function. Mechanosensitivity may have clinical implications for disorders rooted in abnormal mechano-electrical feedback, such as heart failure and atrial fibrillation. Ranolazine is a modulator of Na\textsubscript{v}1.5 function with multiple clinical effects but no definitive mechanism of action. This study demonstrates that ranolazine is an effective inhibitor of Na\textsubscript{v}1.5 mechanosensitivity at the whole cell and single channel level in both cardiac myocytes and cultured cells. We also provide some evidence on the mechanism of ranolazine inhibition of Na\textsubscript{v}1.5 mechanosensitivity. This effect does not require the established ranolazine binding site and appears to require bilayer partitioning. Inhibition of mechanosensitivity by ranolazine decreases excitability of Na\textsubscript{v}1.5 by mechanical stimuli and provides a new mechanism of drug action, with potential for applications in conditions of abnormal mechano-electrical feedback. See p 2698.

Early Results of Fenestrated Endovascular Repair of Juxtarenal Aortic Aneurysms in the United Kingdom

The technique of fenestrated endovascular repair (f-EVAR) of aortic aneurysms has been developed for use in juxtarenal and pararenal aneurysms that do not have an adequate aneurysm neck to allow a standard endovascular repair. Existing literature is a source of optimism, but it has been predominantly from expert operators who have been involved in the development of complex endograft design. It remained unknown if their results could be reproduced in the wider clinical practice. This is an important question, because the use of this technique is expanding rapidly and outside the pioneering centers. The British Society for Endovascular Therapy launched this study with the purpose of establishing nationwide results of f-EVAR without selection or reporting biases. Every center in the United Kingdom with an established f-EVAR service collaborated for this study. Data were collected through the GLOBALSTAR on-line registry. This analysis of early results confirm that, in the United Kingdom, national results of f-EVAR are comparable to those from single-center series. This finding justifies the continued use and evaluation of the f-EVAR by means of a prospective multicenter study. See p 2707.

Exercise Training Attenuates MuRF-1 Expression in the Skeletal Muscle of Patients With Chronic Heart Failure Independent of Age: The Randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging Catabolism Study

Exercise intolerance in chronic heart failure (CHF) is influenced not only by the degree of left ventricular systolic dysfunction but also by peripheral skeletal muscle abnormalities, which commonly develop in advanced CHF and may progress to cardiac cachexia. Despite the clinical importance of muscle wasting in CHF, the molecular mechanisms are still largely unknown, and no specific anticiabatic treatment is currently available. In the Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) study, skeletal muscle biopsies were obtained from the quadriiceps muscles in younger and older CHF patients and in age-matched healthy subjects to analyze whether an important signaling system for intracellular protein degradation called the ubiquitin-proteasome system was activated in heart failure and whether activation was higher with older age. We found that one of the key enzymes that marks structural proteins for protein degradation (MuRF-1) was significantly elevated in muscle biopsies from CHF patients in both age groups. Four weeks of aerobic exercise training reduced the MuRF-1 expression back to normal values. Importantly, the relative improvement did not differ between younger and older CHF patients. Understanding the specific changes causing the catabolic-anabolic imbalance in CHF is an essential first step in the development of pharmaceutical intervention strategies aimed at blocking muscle catabolism in CHF. See p 2716.

Reduced Endoglin Activity Limits Cardiac Fibrosis and Improves Survival in Heart Failure

Heart failure is a major cause of global mortality. Transforming growth factor-β1 (TGFβ1) is a cytokine that promotes cardiac fibrosis in heart failure. Endoglin is a coreceptor that regulates TGFβ1 signaling via downstream effector proteins known as Smads (canonical pathway) or mitogen-activated protein kinases (noncanonical pathway). The extracellular domain of endoglin can be cleaved into the circulation as soluble endoglin (sEng), which may serve as a natural antagonist to TGFβ1 activity. We now report that endoglin expression is increased in failing human left ventricular tissue and in a murine model of thoracic aortic constriction–induced heart failure. Using the endoglin haploinsufficient mouse model, we observed improved survival, limited cardiac fibrosis, and enhanced myocardial capillarity after thoracic aortic constriction. To study the role of endoglin in vitro, loss-of-function studies demonstrated the dependence of TGFβ1 activity on endoglin expression in human cardiac fibroblasts. Paradoxically, adenovirus-mediated overexpression of full-length endoglin also blocked TGFβ1-induced collagen synthesis. Further study showed that levels of sEng were elevated in the conditioned media after treatment with the adenovirus, thereby implicating sEng as a negative regulator of TGFβ1 activity. This observation was confirmed by adenovirus-mediated overexpression of human sEng or treatment with recombinant human sEng in vitro. To begin exploring the utility of sEng as an antifibrotic approach in vivo, treatment with adenovirus-mediated overexpression of human sEng attenuated cardiac fibrosis in wild-type mice after thoracic aortic constriction. Together, these data identify endoglin as an important component of cardiac remodeling and a potentially novel target of therapy in heart failure. See p 2728.

Tumor Necrosis Factor-α–Mediated Downregulation of the Cystic Fibrosis Transmembrane Conductance Regulator Drives Pathological Sphingosine-1-Phosphate Signaling in a Mouse Model of Heart Failure

This study brings forth the novel concept that changes in vascular cystic fibrosis transmembrane conductance regulator expression underlie the enhancement of vascular tone in heart failure. Our investigation additionally shows that this pathophysiological response is widespread, suggesting that it is a global response that may
drive multiorgan dysfunction in heart failure. At the mechanistic level, the cystic fibrosis transmembrane conductance regulator functions as a key regulator of sphingosine-1-phosphate degradation, the modulation of which critically alters myogenic and vascular tone. We conclude that the cystic fibrosis transmembrane conductance regulator represents an unexplored therapeutic target for the improvement of vascular function in heart failure. See p 2739.

**Targeted Deletion of MicroRNA-22 Promotes Stress-Induced Cardiac Dilation and Contractile Dysfunction**

The identification of genes and pathways involved in progression to heart disease is a major challenge and focus in cardiac research. New evidence has established the importance of microRNAs (miRNAs) in controlling cardiac pathophysiology. The relevance of miR-22 to human heart failure has been suggested by the recent demonstration that miR-22 expression was either downregulated or upregulated in human dilated cardiomyopathy and diseased hearts. In the present report, we demonstrate that genetic ablation of the non–protein-coding gene miR-22 in mice impairs cardiac reserve to β-adrenergic stimulation with dobutamine. Here, we show that the absence of miR-22 increases vulnerability to pressure-overload–induced cardiac decompensation characterized by left ventricular dilation and loss of contractile function. The inability of mutant mice to adapt to biomechanical stress was caused in part by restrained expression of genes such as sarcoplasmic reticulum calcium ATPase (Serc2α), LIM domain binding 3 (Ldb3), cardiac LIM protein (Csrp3/Mlp), and Titin encoding calcium handling and other contractile/myofibrillar proteins implicated in human dilated cardiomyopathy and diseased hearts. In this phenotype, we attributed in part to inappropriate inhibition of serum response factor–dependent gene expression in mutant hearts. In addition, we demonstrated that miR-22 inhibits the expression of purine-rich element binding protein B, a transcription factor that opposes control of sarcomeric/cardiomyocytic expression by serum response factor. These results demonstrate the importance of miR-22 as a homeostatic keeper of cardiac gene expression and modulator of cardiac contractile reserve to acute and hemodynamic stress. These results are the first to demonstrate a novel disease mechanism of cardiac pathogenesis involving miR-22. See p 2751.

**Human Genome-Wide Association and Mouse Knockout Approaches Identify Platelet Supervillin as an Inhibitor of Thrombus Formation Under Shear Stress**

Platelets play a central role in ischemic arterial vascular disease, and antiplatelet therapies are mainstays of treatment. The findings in this study identify a novel platelet protein, supervillin, which functions to dampen the early formation of platelet thrombi under high shear stress. Although these results will not alter current management of vascular disease, there are potential clinical implications. Supervillin is an interaction hub for many proteins that regulate cell adhesion and contractility. Drug targeting of supervillin or one of its binding partners in a manner that would decrease platelet adhesion under high shear forces may have antithrombotic benefit for arterial vascular diseases such as myocardial infarction and stroke. This benefit could be especially pronounced in African Americans, who suffer disproportionately from cardiovascular disease. Conversely, drugs that knowingly or unknowingly block supervillin function in platelets could have untoward effects of promoting thrombosis. The shear dependence of the supervillin effect presents an opportunity to develop therapies that differentially affect arterial and venous thrombosis by inhibiting platelet thrombus formation under high shear settings (eg, acute coronary syndromes or percutaneous coronary intervention) without altering the normal hemostatic function of platelets in low-shear veins or microcirculation. Finally, single-nucleotide polymorphisms strongly linked to the causative supervillin variant may be useful as a biomarker for risk of thrombosis or hemorrhage. See p 2762.
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