Drug-Sensitized Zebrafish Screen Identifies Multiple Genes, Including GINS3, as Regulators of Myocardial Repolarization

The ECG QT interval duration is a predictor of mortality in rare familial long-QT syndromes but also in a wide range of acquired heart diseases. QT prolongation can occur as an unintended drug side effect and lead to fatal arrhythmias. This drug side effect has been a major cause of the withdrawal of medications from the market in the last decade. Recent studies in large human cohorts have suggested that many genes regulate the human QT interval, or cardiac repolarization. We and others have shown that cardiac repolarization in the zebrafish bears remarkable similarities to human physiology. We have developed techniques to study cardiac electrophysiology in the zebrafish and performed a genetic screen to aid in the discovery of new genes for repolarization. Using this approach, we confirmed that the recently identified NOS1AP gene regulates cardiac electrophysiological function and performed a drug-sensitized screen for genes affecting repolarization. The results have revealed a network of 15 genes that modulate the response to the QT-prolonging drug dofetilide. One of the genes in this network, GINS3, also was recently found in independent human studies to be associated with QT variation. Identification of these genes may lead to a better understanding of the underlying biology, aid in identification of patients at risk for sudden death, and potentially enable new treatments for susceptible individuals. See p 553.

Quality of Care for Acute Coronary Syndrome Patients With Known Atherosclerotic Disease: Results From the Get With the Guidelines Program

Patients with prior atherosclerosis in 1 or more vascular territories (coronary, cerebrovascular, or peripheral arterial) who present with acute coronary syndromes have high cardiovascular risk. Whether those patients receive evidence-based therapies to a similar or lesser extent than those without prior atherosclerosis is unknown. To answer this question, we examined 143 999 patients participating in the Get With the Guidelines–Coronary Artery Disease database. Preexistent atherosclerosis in 1, 2, or 3 vascular territories was common (26%, 5%, and 0.6%, respectively). As expected, compared with patients without prior vascular disease, patients with prior vascular disease were older and had more comorbidities. They were less likely to undergo coronary revascularization and had longer duration of hospital stay and higher in-hospital mortality. After adjustment for clinical and hospital characteristics, compared with patients without prior vascular disease, those with prior vascular disease had higher mortality and were less likely to receive 3 guideline-recommended treatments (lipid-lowering therapy, smoking cessation counseling, and angiotensin-converting enzyme inhibitor for left ventricular dysfunction) but were equally likely to receive other treatments, such as aspirin and β-blockers. Patients with prior vascular disease who present with an acute coronary syndrome are an easily identifiable patient group that may have significant benefit from interventions targeted to those 3 evidence-based treatments. See p 560.

Targeted Ablation of PINCH1 and PINCH2 From Murine Myocardium Results in Dilated Cardiomyopathy and Early Postnatal Lethality

Cardiomyocytes communicate with their surrounding microenvironment through costameres. In both humans and animal models, dysfunction of costamere adhesion leads to cardiomyopathy and heart failure. Adhesion between cardiomyocytes and the extracellular matrix at the costamere is mediated by integrin-β1 receptor and its associated complex. Engagement of integrin with extracellular matrix leads to recruitment and formation of a cytoplasmic focal adhesion complex that links integrins to the actin cytoskeleton and other intracellular pathways. This complex is composed of integrin-linked kinase, Parvin, and PINCH proteins. Two PINCH proteins, PINCH1 and PINCH2, have been described in mammals and share high homology. Both PINCH1 and PINCH2 are expressed in most tissues and organs, including myocardium. However, whether PINCH is required in normal myocardium or for postinjury healing of myocardium has not been addressed. To explore the functional role of PINCH in cardiomyocytes, we generated several mouse lines in which PINCH1 and PINCH2 are singly or doubly ablated in myocytes. Analysis of these mouse models has demonstrated essential roles for PINCHs in myocardial growth and maturation, as well as remodeling in response to injury, and highlights the importance of studying the role of PINCHs in human cardiac remodeling and cardiomyopathy. See p 568.

Impact of Myocardial Fibrosis in Patients With Symptomatic Severe Aortic Stenosis

Aortic valve stenosis remains a diagnostic and therapeutic challenge, particularly in the elderly. In patients with aortic stenosis, left ventricular hypertrophy compensates for pressure overload. Left ventricular hypertrophy may be accompanied by interstitial myocardial fibrosis starting at the subendocardial layers and progressing toward replacement fibrosis. Importantly, fibrosis also may have an impact on patient outcome after aortic valve replacement. In a clinical follow-up study, we assessed the degree of myocardial fibrosis and its influence on myocardial function and clinical outcome after aortic valve replacement in patients with symptomatic severe aortic stenosis. The findings support a preoperative diagnostic approach that focuses on the structural abnormalities of the left ventricular myocardium. In this context, myocardial replacement fibrosis seems to be the critical abnormality that can be visualized directly with late-enhancement cardiac magnetic resonance imaging in most of these patients. This type of fibrosis has a profound impact on the long-term clinical outcome but remains undetected by standard echocardiographic examination. However, the longitudinal displacement of the mitral ring can be measured reliably during standard echocardiography, captures the functional consequences of myocardial fibrosis, and predicts functional improvement after aortic valve replacement. Thus, the evaluation of mitral ring displacement also may prove valuable for routine preoperative risk assessment. See p 577.

Subclinical Brain Embolization in Left-Sided Infective Endocarditis: Results From the Evaluation by MRI of the Brains of Patients With Left-Sided Intracardiac Solid Masses (EMBOLISM) Pilot Study

Infective endocarditis is a disease characterized by high morbidity and mortality. In patients with left-sided infective endocarditis, the occurrence of acute brain embolization has significant implications for prognostication and clinical decision making. In this preliminary study, we found that systematic use of magnetic resonance imaging of the brain detected the presence of subclinical brain embolization in a substantial proportion of patients in whom there was no clinical
evidence of stroke. This finding was particularly prevalent among patients with *Staphylococcus aureus* as the causative organism. Patients with clinical stroke and those with subclinical brain embolization had similar baseline characteristics and survival, suggesting that clinical stroke and subclinical brain embolization may have similar clinical implications. However, patients with clinical or magnetic resonance imaging evidence of brain embolization had significantly higher mortality at 3 months than those without such findings. No patient with acute brain embolization who underwent cardiac surgery suffered a postoperative neurological complication. If these findings are confirmed in larger studies, brain magnetic resonance imaging may assume a wider role with respect to treatment decisions in patients with left-sided infective endocarditis. See p 585.

**Enzyme-Sensitive Magnetic Resonance Imaging Targeting Myeloperoxidase Identifies Active Inflammation in Experimental Rabbit Atherosclerotic Plaques**

Inflammatory cells, particularly macrophages, are believed to underpin the stability of atherosclerotic plaques, promoting plaque rupture and subsequent life-threatening thrombosis. The present study represents a novel approach in imaging inflammation in atherosclerosis by imaging macrophage function and the activity of a key effector enzyme, myeloperoxidase, which is known to trigger oxidative reactions. Unlike measurement of the presence of phagocytes, measurement of myeloperoxidase activity in plaques is likely to have greater specificity to identify vulnerable plaques. This molecular imaging technology can potentially localize plaques with active inflammation before devastating thromboembolic events occur. See p 592.

**Sirolimus-Eluting Stent Treatment at High-Volume Centers Confers Lower Mortality at 6-Month Follow-Up: Results From the Prospective Multicenter German Cypher Registry**

Drug-eluting stents remain a very effective method for the treatment of coronary artery disease. In light of the observed small increased incidence of late thrombosis after implantation of drug-eluting stents, which may manifest by death or large infarctions, certain safety issues should be considered in the complex process of patient selection for patients subjected to this kind of revascularization, implantation techniques, and postprocedural medical therapy. In the present analysis, which included 8201 patients from the multicenter prospective German Cypher Registry who were treated with sirolimus-eluting stents, we found that hospitals with a lower volume of sirolimus-eluting stent–based procedures had significantly higher rates of death and myocardial infarction at 6-month follow-up than high-volume centers. After adjustment for different baseline factors known to be associated with higher mortality and infarction, institutional volume remained an independent risk predictor for death and infarction at 6 months (odds ratio 1.85, 95% confidence interval 1.31 to 2.59, *P*<0.001 for low-volume centers; odds ratio 1.69, 95% confidence interval 1.29 to 2.21, *P*<0.001 for intermediate-volume centers). It was also obvious that patient selection, procedural details, and postprocedural medication differed significantly according to hospital volume, with a stricter implementation of current recommendations in high-volume centers. See p 600.

**Tumor Suppressor Ras-Association Domain Family 1 Isoform A Is a Novel Regulator of Cardiac Hypertrophy**

Understanding the molecular mechanisms of hypertrophy is key in elucidating the pathogenesis of heart failure. Our study is based on 2 premises: first, many factors that positively mediate hypertrophy have been identified in recent years, but little is known about molecules that counteract and therefore limit cardiac growth. Second, a series of mutations in genes of the Ras-signaling pathway have recently been identified, which associate certain cancers with hypertrophic cardiomyopathy (eg, in Noonan and Costello syndromes). This led us to hypothesize that negative regulators of the Ras pathway may also limit cardiac growth in common conditions such as pressure overload. One such negative regulator in cancer is the recently described tumor suppressor protein Ras-association domain family 1 isoform A (RASSF1A). We therefore investigated the role of this molecule in negatively regulating myocardial hypertrophy. We subjected mice with genetic ablation of *Rassfl* gene to transverse aortic constriction. A massive increase in the hypertrophic response, fibrosis, and left ventricular dilatation were observed in these animals. We further showed that RASSF1A acts through the inhibition of Ras at the level of Ras/Raf1 interaction, thus blocking the downstream extracellular regulated kinase 1/2 signaling pathway. Furthermore, a significant downregulation of RASSF1A expression by ≈50% was observed in failing human hearts, indicating its involvement in the development of heart failure. Our findings establish RASSF1A as a novel inhibitor of cardiac hypertrophy both in mouse and human and may provide opportunities for the development of novel therapeutic strategies for heart failure by targeting this molecule. See p 607.

**Response Gene to Complement 32, a Novel Hypoxia-Regulated Angiogenic Inhibitor**

We and others have suggested that response gene to complement 32 (RGC-32) is involved in cell cycle regulation. Our data prove the novel ability of the expression of RGC-32 to increase in hypoxia/ischemia and to inhibit angiogenesis in endothelial cells. Ischemia is characterized by reduced blood supply to the organs. Although angiogenesis occurs in response to ischemia, angiogenesis induced by natural compensatory processes is often inadequate. Many unsuccessful clinical trials have tested the proangiogenic potential of vascular endothelial growth factor or fibroblast growth factor, and the role of growth factor feedback molecules in attenuating angiogenic response in ischemic disease is not completely understood. RGC-32 as a downstream gene induced by hypoxia/ischemia and vascular endothelial growth factor possesses angiogenesis capability. Inhibiting the negative feedback of vascular endothelial growth factor is a significant potential angiogenic therapy. In addition, given that angiogenesis is an important process in tumor growth, antiangiogenic factors can block the fundamental requirements of a tumor. Thus, RGC-32 has clinical application for tumor retardation through its inhibition of angiogenesis. We have demonstrated that injection of RGC-32 in the xenograft tumor model resulted in reduced growth of blood vessels that is consistent with reduced colon tumor size. Therefore, it is conceivable that RGC-32 provides a new target for ischemic disorder and tumor therapies. See p 617.

**Functional Lecithin: Cholesterol Acytransferase Is Not Required for Efficient Atheroprotection in Humans**

Population studies clearly demonstrate that a low plasma high-density lipoprotein cholesterol (HDL-C) concentration is a strong predictor of future coronary heart disease. Genetically determined low HDL-C states, however, may be associated with a widely variable cardiovascular risk. In the present study, we show that individuals with a defect in cholesterol esterification, due to mutations in the gene coding for the lecithin:cholesterol acyltransferase enzyme, have low HDL-C levels but do not present with enhanced
preclinical atherosclerosis, as assessed by measuring carotid intima-media thickness. This finding complements previous observations on the lack of preclinical atherosclerosis and premature coronary heart disease in other genetic conditions leading to reduced plasma HDL-C levels, like the apolipoprotein A-I Milano mutation. It illustrates that HDL-C levels per se do not necessarily reflect the atheroprotective potential of HDL-C and highlights the need for novel tools for cardiovascular risk prediction in individuals with low HDL-C. Moreover, it challenges the notion that lecithin:cholesterol acyltransferase is required for effective atheroprotection and suggests that, despite positive effects on plasma HDL-C concentration, elevating lecithin:cholesterol acyltransferase expression or activity is not a promising therapeutic strategy to reduce cardiovascular risk. See p 628.