Blocked heart

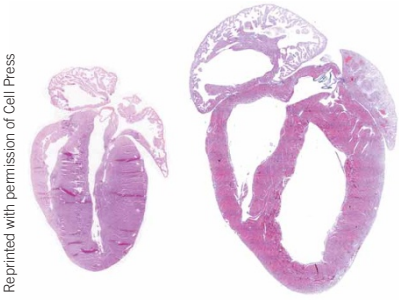
β-adrenergic receptor blockers, arguably the most important class of drug for heart failure, have faced a long uphill journey into the clinic, culminating in the mid-1990s with studies by Waagstein *et al.* (*Lancet*, **342**, 1441-1446; 1993) and Packer *et al.* (*N. Engl. J. Med.* **334**, 1349-1355;1996).

When, in the 1960s, these compounds were first considered for clinical use, the common view was that heart failure therapy should aim to bolster β-adrenergic receptor signaling—rather than interfere with it. Stimulation of β-adrenergic receptors by catecholamine neurotransmitters of the sympathetic nervous system increases heart rate and cardiac muscle contraction, and early studies had indicated that failing hearts suffered from a loss of adrenergic neurotransmission.

A series of human studies, beginning more than 25 years ago, eventually undermined this classical view. Failing hearts, for instance, were shown to have increased adrenergic activity, and β–blocking agents improved myocardial function. Waagstein *et al.* and Packer *et al.* buttressed this proof of concept work in their large-scale studies showing that β-blockers benfitted patients with chronic heart failure.

Although research over the past decade has revealed much about how β-adrenergic receptors signal in the heart, including their regulation of calcium flux, the puzzle of how β-blockers counteract heart failure has not yet been fully solved. One area of heated debate revolves around the relative benefits of antagonists of specific receptor subtypes versus non-specific antagonists.—*MB*

Big heart



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Enlargement of the heart (cardiac hypertrophy) is an adaptive response to stresses such as hypertension, heart attack or arrhythmia. Chronic, sustained hypertrophy, however, can result in heart failure. In 1998, Molkentin *et al.* (*Cell* **93**, 215–228) exposed the molecular machinery underlying cardiac hypertrophy by showing how elevated intracellular calcium leads to the reprogrammed gene expression characteristic of this disease. The intermediary, they found, is the calcium-sensitive phosphatase calcineurin.

Whereas transient changes in calcium levels within cardiac muscle cells control muscle contraction, a sustained elevation in calcium triggers the hypertrophic response, in which each cell gains dramatically in size. Wholesale changes in gene expression, with adult tissue re-expressing fetal versions of myosin and actin, are also key characteristics of hypertrophy. Molkentin *et al.* were the first to define the link between these two events. To do this, they constructed a transgenic mouse expressing activated calcineurin specifically in the heart—these mice develop cardiac hypertrophy and heart failure (normal heart on left, transgenic on right). They also showed that activated calcineurin dephosphorylates a transcription factor, NF-AT3, enabling its translocation to the nucleus. Once there, NF-AT3 interacts with another factor, GATA4 (a known hypertrophy signal), to activate the new expression program.

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Subsequent work identifying endogenous inhibitors of calcineurin signaling in the heart has bolstered calcineurin's standing as a central mediator of hypertrophy. A better understanding of these molecular 'nodal points' where various hypertrophic stimuli converge may lead to new targeted therapies that stop heart failure in its tracks. —*CW*

Statins grow stronger

Over 11 million Americans take one of several cholesterol-lowering drugs called statins, and recommendations from a US government health advisory board suggest that is not enough—36 million people could benefit from them. But the recommendations were not always so enthusiastic. That changed in 1994, with the publication of a trial of 4,444 patients showing definitively that Simvastatin benefitted patients with coronary heart disease (*The Lancet*; **344**, 1383–1388).

Before this study, clinicians sometimes prescribed cholesterol-lowering drugs, but patients found them difficult to tolerate and trials showed no overall reduction in mortality rates; through the early 1990's top cardiologists weighed in against taking drugs to control cholesterol. The 1994 trial showed that Simvastatin was safe and that it reduced the risk of coronary events, revascularization procedures and—most dramatically—death.

Since 1994, large-scale trials, involving over 50,000 patients in total, have expanded the patient roster. For instance, Simvastatin reduces risk in patients with cardiovascular disease even if they have below-average cholesterol levels; and other studies have suggested that lowering cholesterol levels below average also benefits individuals without known atherosclerosis. While the 20th century lifestyle has probably pushed cholesterol levels above historical averages, statins are also now known to have effects other than cholesterol lowering. These effects range from altering endothelial cell function to reducing the inflammatory response. Much of this breadth is due to the inhibitory action of statins on HMG-CoA reductase, which catalyzes not only cholesterol synthesis but also the production of lipids that latch on to certain signaling proteins, such as Rac and Rho. —*CS*

Sarcomeres and septation

The last decade has seen an explosion of information about the genetic basis of cardiac development, spurred in part by the identification of single-gene mutations that lead to congenital heart failure. Among the many mutations that have been reported over this period, two stand out as particularly strong contributions to the field.

In 1994, Thierfelder *et al.* (*Cell* 77, 701–712) established that mutations in α-tropomyosin and cardiac troponin T cause familial hypertrophic cardiomyopathy (FHC)—a disorder characterized by increased myocardial mass with myofibrillar disarray. Mutations in the gene encoding the cardiac myosin heavy chain were known to cause this disorder, but the discovery that mutations affecting other proteins of the contractile machinery produced a similar phenotype led to the idea that FHC is a disease of the sarcomere, instead of a nonspecific dysfunction of cardiac myocytes. The subsequent identification of FHC-causing mutations in other sarcomere proteins has substantiated this assertion.

In 1998, Schott *et al.* (*Science* **281**, 108–111) showed that mutations in the gene for the transcription factor *NKX2.5* lead to defects in septation—the division of the primordial atrium and ventricle into four chambers. Previous data had implicated invertebrate homologs of *NKX2.5* in heart development, but this study was the first to flush out a gene specifically involved in atrial septation, a process defective in 1 out of 1,500 births. In addition, this study profoundly influenced the study of cardiac development, stimulating the search for the targets of *NKX2.5*. —*JCL*