HEART DISEASE

Signaling Path May Lead to Better Heart-Failure Therapies

Like the waistband in your favorite old pajamas, overstressed hearts often lose their elasticity, becoming saggy and stretched out. Hearts in this state, called congestive heart failure, are ineffective at pumping blood and are prone to arrhythmias that cause sudden death. With 500,000 new cases of heart failure diagnosed each year in the United States alone, cardiologists who treat the problem are eager for new and better drugs. They may soon get their wish.

In a paper published in today's issue of *Cell*, biologist Eric Olson of the University of Texas Southwestern Medical Center at Dallas and his colleagues report a big step toward uncovering the underlying pathology of congestive heart failure. They have found an internal signaling pathway in cardiac muscle cells that, when pushed into overdrive, can cause heart failure in mice. What's more, the team showed that the immunosuppressive drug cyclosporin A inhibits the pathway, blocking heart failure in the animals.

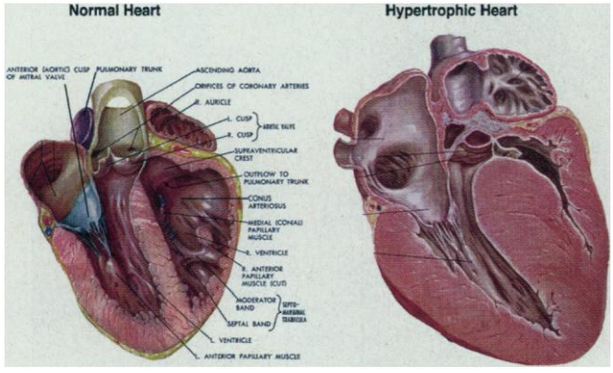
"It is quite exciting," says Seigo Izumo, a cardiologist at Harvard Medical School in Boston. "This paper begs for the examination of this [approach] in a different animal model, and if that is promising, in the human condition." But, he cautions, "it is too early to become too optimistic," because no one knows yet whether faults in this pathway are a common cause of human heart failure.

Heart failure develops when the heart tries to compensate for abnormal stress on its muscular wall by growing bigger. That enlargement "starts out being OK," and boosting the heart's power, says cardiologist Michael Bristow, of the University of Colorado Health Sciences Center in Denver, "but it goes too far." The muscle cells get long and thin, and like spent elastic, they fail to contract properly, resulting in sluggish blood flow, shortness of breath, and buildup of fluids in tissues. Fibrous deposits form on the heart's walls and can cause arrhythmic beating and sudden death.

A variety of stresses can cause this heart muscle hypertrophy, as it is called, ranging from a congenitally weak heart muscle to a narrowed aortic valve, high blood pressure, or death of parts of the muscle in a heart attack. Most of these causes seem to have one thing in common: They raise calcium levels in heart cells. How that might effect hypertrophy was unclear, however.

That's where Olson's work comes in. While studying a protein called GATA4, a DNA binding protein that turns on heart cell genes during hypertrophy, his team found that GATA4 binds to a protein called NF-AT3. That was exciting, Olson recalls, because NF-AT3 belongs to a family of proteins that regulate genes in response to calcium levels in activated T cells of the immune system. The discovery, he says, "suggested how [calcium and hypertrophy] could be interlinked."

In T cells, a calcium-sensitive enzyme called calcineurin activates NF-AT proteins by removing a phosphate group they carry. This allows the proteins to enter the nucleus and regulate genes. The researchers thought the same thing might happen when calcium levels rise in stressed heart cells, allowing NF-AT3 to go to the nucleus, link up with GATA4, and turn on the genes for hypertrophy.



Pumped up. In congestive heart failure *(right)*, the heart muscle becomes much thicker than normal *(left)*.

Two experiments in cultured heart cells suggested they were right. Such cells respond to hypertrophy-triggering hormones such as angiotensin II by turning on genes, growing larger, and beefing up their contractile machinery. The team found that the immunosuppressant drugs FK506 and cyclosporin A, which inhibit calcineurin's action, blocked these changes in cultured heart cells. They also showed that NF-AT3 and GATA4 together turn on one of the genes that comes on in heart cells during hypertrophy. Those results mean that, at least in these cultured cells, NF-AT3 is activated by calcineurin and works with GATA4 to turn on genes.

The next key issue was whether this signaling system triggers heart failure in animals. To find out, the researchers created mice carrying a mutant calcineurin gene that causes their hearts to make a form of the enzyme that turns on at birth and keeps the NF-AT3 pathway active regardless of calcium levels. To the group's surprised satisfaction, the mice "recapitulate every physiological and pathological aspect of human heart failure," says Olson, "including extensive fibrosis, arrhythmias, and sudden death." What's more, mice treated with cyclosporin A from an early age showed no signs of disease.

"This gives strong hope" that drugs such as cyclosporin might halt or even reverse congestive heart failure in humans, says cardiologist Michael Schneider of Baylor College of Medicine in Houston. But he and others say that hope should be tempered with caution. Although calcineurin action is clearly responsible for the heart failure in the Olson team's mice, says Izumo, "an unknown question is how much of a role this pathway plays in other models of hypertrophy or failure, and especially in the human condition." One way to address that question, he says, is to test the effect of cyclosporin A in other mouse models of the condition, many of which are based on genetic mutations in heart proteins.

If cyclosporin works in these animals, it may warrant a test in humans, says Izumo. Heart failure is serious enough to justify the risks of immunosuppression from cyclosporin, he argues, and as the drug is already in use for organ transplants, heart failure trials could begin without a lengthy federal approval process.

In the longer term, the discovery may lead to better drugs for heart failure, says Jerry Crabtree of Stanford University Medical Center, who studies NF-AT signaling in the immune system. Because GATA4 is a heart-specific gene regulator, screening for small molecules that break its interaction with GATA4 might lead to heart-specific drugs with few side effects, says Crabtree. "I would be very, very surprised if some drug company didn't immediately jump on this."

An important issue is whether blocking the calcineurin pathway merely halts or actually reverses the hypertrophy. People diagnosed with heart failure generally have advanced disease, says Bristow, so "what we really need is to be able to turn the clock back." But even if that can't be done, Bristow notes that blood tests being developed can detect cardiac hypertrophy in its early stages and will soon be used to screen people who are at risk. "I guarantee within the next 5 years this will be a viable approach," he says. If that prediction comes to pass, calcineurin- or GATA4-blocking drugs may be part of the prescription for people in the early stages of heart failure.

–Marcia Barinaga