Shrinking old hearts

By Lev Osherovich, Senior Writer

Boston researchers have discovered a blood-borne protein, growth differentiation factor 11, that can reverse age-related cardiac hypertrophy in mice.¹ The protein could be used as a therapeutic agent once its long-term effects are understood.

Cardiac hypertrophy, the pathological enlargement of one or more ventricles, can occur in old age or in response to chronic hypertension and myocardial infarction (MI). Chronically enlarged hearts develop fibrosis and eventually fail.

Cardiologists primarily try to prevent cardiac hypertrophy by reducing hypertension and the risk of MI. However, hypertrophy also may be reversible.

When triggered by hypertension or other stress, cardiomyocytes can become larger. Conversely, when demand on the heart falls, heart muscle cells can shrink.

“When you remove the growth trigger, the heart is capable of remarkable plasticity back to its normal state,” said Joseph Hill, professor of medicine and chief of cardiology at **The University of Texas Southwestern Medical Center**.

Hill said a variety of intracellular signaling pathways act as “brakes and accelerators in heart growth,” but the upstream factors that regulate these pathways are not well understood.

Now, a team co-led by Amy Wagers and Richard Lee has found evidence that growth differentiation factor 11 (GDF11) is a master regulator of heart size.

Wagers is a professor of stem cell and regenerative biology at **Harvard University** and an investigator at the **Howard Hughes Medical Institute**. Lee is a professor of medicine at **Brigham and Women’s Hospital** and **Harvard Medical School**.

The team reported that GDF11, a secreted member of the transforming growth factor- β (TGFB; TGF β) family, wards off cardiac hypertrophy in young mice and can reverse the condition in old mice.

Wagers and Lee discovered GDF11’s role using heterochronic parabiotic mice, in which an old and young mouse are surgically connected so that they share a circulatory system.

Wagers previously used this technique to study the effect of circulating factors that promote tissue regeneration, which involves the proliferation of cells rather than changes in cell size. The adult heart does not typically regenerate new cardiomyocytes to replace damaged ones, so Wagers did not expect to see an effect from youthful serum on the heart itself.

“We usually focus on tissues that repair themselves well during youth but don’t do so well in old age,” said Wagers. “I thought the heart would not respond, since it’s not known for its regenerative capacity. I was dramatically wrong in this hypothesis.”

Young blood

Wagers and Lee surgically joined old and young mice and kept the paired mice immobilized for four weeks, then separated the animals to examine cardiovascular function.

Ordinarily, old mice have enlarged hearts compared with younger controls. However, after sharing blood with young mice, the older animals had smaller, more youthful-looking hearts and smaller cardiomyocytes than did controls (old mice connected to other old mice).

To find the factor responsible for the heart-rejuvenating effect of heterochronic parabiosis, the team analyzed the metabolic and proteomic profiles of old and young mice and converged on GDF11.

Young mice had high GDF11 levels, whereas old ones had low levels. In cell culture, murine cardiomyocytes with recombinant GDF11 had lower growth rates than did saline-treated controls. Injection of recombinant GDF11 into old mice reduced heart size and molecular markers of cardiac hypertrophy compared with saline.

Results were reported in *Cell*.

Wagers said her next step is to learn more about the basic functions of GDF11 in mice and humans.

“Not a lot is known about GDF11, which is a member of a broad superfamily of molecules with transforming growth factor- β and bone morphogenetic protein (BMP) homology,” she said. “We want to understand how GDF11 is regulated during human aging.”

Along these lines, the team reported that in human cardiomyocytes, recombinant GDF11 activates components of the TGF β signaling pathway and controls the activity of transcription factors involved in cardiac muscle remodeling.

Junichi Sadoshima, professor of cell biology and molecular medicine at the **University of Medicine and Dentistry of New Jersey**, said it would be necessary to characterize the functional effects of reversing cardiac hypertrophy with GDF11.

“They particularly look at the hypertrophy but they don’t look much at cardiac function,” said Sadoshima. In patients with cardiac hypertrophy, “diastolic heart failure is a significant problem, but [the researchers] don’t show whether this is improved by young serum or parabiosis. Old hearts are susceptible to stress and reperfusion injury, so it would be nice to see functional assays” of these conditions.

Hill said it was unclear whether GDF11 could reverse more severe forms of cardiac hypertrophy than those caused by aging.

“Pathological remodeling in the heart is not just about cell growth,” said Hill. “They should evaluate GDF11’s effect on fibrosis and other elements” of advanced heart disease.

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—Amy Wagers, Harvard University

Stressing out

Wagers said she indeed plans to test the effect of GDF11 in a variety of cardiac injury and stress models. Her ultimate goal is to make a recombinant version of GDF11 that could be administered to patients. The biggest challenges will involve improving the protein's specificity and stability.

She noted GDF11 is a close homolog of myostatin (GDF-8), a blood-borne factor encoded by the gene *MSTN* that inhibits growth of skeletal muscle.

Companies previously have tried to block GDF-8 signaling to promote skeletal muscle regeneration in Duchenne muscular dystrophy (DMD) and muscular atrophy.

The most advanced GDF-8 inhibitor was **Acceleron Pharma Inc.**'s activin receptor type 2b (ACVR2B) antagonist ACE-031, which failed a Phase II trial in DMD in 2011 because of vascular safety concerns. In May, partner **Shire plc** handed rights to ACE-031 back to Acceleron.

"ACE-031 is a receptor for GDF-8 that is soluble," said Acceleron CSO Ravi Kumar. "We have published that it also binds to GDF11."

Kumar said development of ACE-031 was on hold for strategic reasons. Further details were not disclosed.

In 2010, **Amgen Inc.** suspended development of AMG 745, a GDF-8 inhibitor that was in Phase I testing for muscular atrophy.

It is unclear whether ACVR2B is the principal receptor for GDF11 *in vivo*, but one possibility is that the vascular side effects of ACE-031 resulted from cross-inhibition of GDF11.

A related concern is whether interaction of GDF11 with ACVR2B or related receptors would shrink muscles other than the heart.

"The question is whether GDF11 has effects in other tissues," said Hill. "If GDF11's receptor is expressed in other tissues, you need to see if GDF11 has effects there."

Testing the effects of long-term GDF11 treatment may be difficult because the protein has poor solubility and stability.

"These proteins are notoriously hydrophobic and very hard to work with," said Kumar. "They are very short proteins and have a very short half-life."

"The problem with administering GDF11 is that it's probably unstable or not long-lasting," added Sadoshima. "It would be very difficult to keep it at high levels of circulation."

"You might need to administer this chronically," said Hill. "The ideal thing would be a small molecule agonist of cardiac-specific receptors" that mimics the effect of GDF11 but has better pharmacodynamics.

Brigham and Women's Hospital has filed a patent on the therapeutic use of GDF11 in heart disease. That patent is available for licensing.

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