Developing a Transcriptional Roadmap to Prevent and Reverse Left Ventricular Hypertrophy

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At Houston Methodist's Center for Bioenergetics, laboratory mice are helping to unravel the complex intercellular mechanisms regulating structural changes in the heart. Like nearly a third of American adults,[1] these mice have high blood pressure. Left unchecked, the extra pressure will cause these murine hearts to thicken in a condition called left ventricular hypertrophy (LVH), with potentially fatal consequences.

Erin Reineke, Ph.D., hopes to prevent that. She's looking deep inside the cells of the mice's hearts to pinpoint the minute metabolic and transcriptional changes that foreshadow more dramatic structural alterations. If she can map out the transcriptional pathways leading to LVH, researchers may be able to develop therapies that target specific stages, stopping or even preventing heart thickening. Ultimately, Reineke's work could change the way physicians treat LVH in humans, leading to more personalized preventative options to preserve heart function. In a review article in the *Methodist DeBakey Cardiovascular Journal*, Reineke and colleague Deokhwa Nam, Ph.D., examine the latest findings in this new field of translational research.

THE PLOT THICKENS

Like any other muscle, the heart responds to pressure by growing. (Pressure, for the heart, can include diabetes, obesity, and—most often—hypertension.) However, unlike gains at the gym, a thickened heart muscle is not necessarily a good thing. When the left ventricle thickens in LVH, there's not as much room in the chamber to fill up with blood. Moreover, the muscle loses elasticity, requiring more effort to pump less blood out into the arteries. Ultimately, patients with LVH are at risk of heart attack, stroke, arrhythmia, and sudden cardiac death. In fact, LVH is the number one predictor of negative cardiovascular outcomes in patients with hypertension.[2]

Unfortunately, LVH is a stealthy killer; its early symptoms are so subtle that they're often missed until the changes are irreversible. An individual may walk around with mildly elevated blood pressure for years before a physician discovers LVH on an echocardiogram. By that point, it's usually too late to do much about it. However, research shows that—when identified early enough—hypertrophy can be stopped, even reversed.

POINT OF NO RETURN

The path from hypertension to LVH does not go straight from point A to point B. "Hypertrophy is initially adaptive," Reineke explains. "With increased load, there's an increased demand for ATP right away, so the cardiomyocytes upregulate metabolic processes." The first change is an increase in glucose uptake. This initial response is dictated by rapid second messenger signaling and is completely reversible. If the stress is removed, the heart switches back to oxidative glycolysis of fatty acids. The heart may grow slightly, but it's not too late to turn the process back around.

However, the real danger comes when that pressure is not removed. Under long-term stress, the heart switches to what Reineke calls "survival mode." Unable to pump enough oxygenated blood to meet the heart's increased oxidation demands, cardiomyocytes undergo massive genetic and transcriptional changes. Essentially, the heart reverts to its fetal gene profile, switching to anaerobic fatty acid metabolism (just like the fetal heart uses in the low-oxygen environment of the womb). It's not the ideal power source for the adult heart. To Dr. Dale Hamilton, M.D., director of the Center for Bioenergetics, fatty acids are the diesel to glucose's high-octane fuel. "The diesel has its advantages, but it's not quite as powerful," he says.

Unfortunately, once these cellular mechanisms change, there's no going back. "Long-term changes like those acquired during cardiac failure are, at their root, driven by transcriptional changes," Reineke says. "Once you get long steady-state major reorganization of those transcriptional networks, it's really hard for a cell to go back or change its signaling without removal of the stress. And so, in many cases—downstream of diabetes or obesity—the stress isn't going away. It's being driven by constrictive changes to blood vessels or atherosclerosis. Without removing those, you make major changes to the cellular background. Even if you treat the stressor acutely, you may relieve some of the stress, but the underlying cell structure is still changed for the worse in most cases."

This so-called "point of no return" coincides with irreversible LVH. Although researchers have yet to identify the exact relationship, studies show that "metabolic and hypertrophic changes… are connected by shared transcriptional regulators" so that "long-term changes to one ultimately affect the degree of the other."[3] This makes teasing out the complex roadmap of intercellular adaptations all the more important when it comes to preventing LVH.

BENCH TO BEDSIDE

That's where Reineke and her mice come in. In the lab, Reineke induces hypertension by surgically constricting the mice's aortas. By monitoring metabolic and transcriptional changes in hypertensive-mouse cardiomyocytes before LVH sets in, Reineke hopes to pinpoint steps that can eventually be targeted by pharmaceuticals. Her research is an early step in bringing such novel therapies to the bedside. "We need to understand the different stages of the cellular background, then consider how to best treat patients," Reineke says.

Fortunately, research is already underway to identify targets. As Nam and Reineke explain in their article, potential targets of transcriptional regulation break down into three tiers. Tier one includes transcription factors, which are the most specific but also fairly difficult to manipulate with current drugs. Tier two comprises most coactivators and corepressors; they're somewhat less specific in that they interact with multiple transcription factors, making them the middle men that regulate pathways instead of specific gene expression. Promisingly, researchers have had success with tier two targets in cancer clinical trials and cardiovascular disease studies in animals. Finally, tier three includes the least specific targets, such as chromatin modifiers and general transcription mechanisms. Treatments that affect these targets could prove useful for genes that are modified in groups during cardiac stress.

Of course, the key to translating this basic research to usable treatments lies in correlating these intercellular changes with clinical biomarkers. "If we can figure out how to detect a stressed heart before remodeling occurs, perhaps by looking for early changes and increased metabolism of certain substrates, we might be able to treat the heart to prevent downstream effects such as LVH," Reineke explains.

Hamilton echoes her sentiments. "Conceptually, we are identifying genes in metabolism that are starting to change the response to pressure before there is injury to the heart. So if we know those, we can start looking at clinical samples. Maybe we can find markers that we can measure in a blood sample or tests such as cardiac metabolic imaging, similar to a PET scan for cancer," he says. "We're doing PET scans in mice to see if they're using fatty acids or glucose. If we could do those things clinically and know that there's a switch happening in the heart, then there are therapies that could be developed to change and optimize that fuel."

So what does that mean for LVH prevention in the future? Hamilton envisions a scenario where at-risk patients are identified by mild but persistent increases in blood pressure. Rather than waiting to see if the hypertension worsens enough to cause physical symptoms—by which time LVH is already established—physicians could order stress tests and imaging to quantify cellular changes before the muscle begins to thicken. Then they could prescribe treatments targeting specific transcriptional switches at key times, preventing intercellular reorganization. Depending on the patient, these treatments could prevent, stop, or even reverse LVH.

Transcriptional therapies would be a key component of personalized cardiovascular medicine, giving physicians the ability to finely tune treatments for each individual. However, we're not there yet. Piecing together the puzzle of how the heart responds to stress will require collaboration between bench researchers like Reineke, translational researchers like Hamilton, and clinicians. Working together, they are developing the tools to identify at-risk patients years before LVH so that fewer people will reach that point of no return.

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Laura Gerik is assistant managing editor at the *Methodist DeBakey Cardiovascular Journal.*

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