# Animal studies reveal new route to treating heart disease

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Scientists at Johns Hopkins have shown in laboratory experiments in mice that blocking the action of a signaling protein deep inside the heart's muscle cells blunts the most serious ill effects of high blood pressure on the heart. These include heart muscle enlargement, scar tissue formation and loss of blood vessel growth.

Specifically, the Johns Hopkins team found that their intervention halted transforming growth factor beta (TGF-beta) secretion at a precise location called cell receptor type 2 in cardiac muscle cells. Blocking its action in this cell type forestalled pathways for hypertrophy, fibrosis, and angiogenesis by stopping the unbridled TGF-beta signaling, which is typically observed in heart failure, in all other non-muscle types of cells in blood vessels and fibrous tissue. However, blocking TGF-beta signaling in non-muscle cells did not stop disease progression.

In several dozen different experiments, using genetically altered mice or chemicals to selectively block different TGF-beta pathways, researchers were able to pinpoint where the signaling protein had its greatest impact on heart function and determine how its unimpeded activity promoted heart disease.

"Now that we know about the pivotal and specific bad roles played by TGF-beta in a common form of heart disease, we can try to mimic our lab experiments to develop cell-specific drug therapies that stop the chain reactions in the heart muscle at the TGF-beta type 2 cell receptor location," says senior study investigator and cardiologist, David Kass, M.D. Kass is a professor at the Johns Hopkins University School of Medicine and its Heart and Vascular Institute.

The Kass team study, to be published in the June edition of the Journal of Clinical Investigation, is believed to show the first evidence of how TGF-beta is stimulated differently by various cell types in the heart and which resulting pathways promote heart failure, the most common kind of heart disease. Nearly 6 million Americans are estimated to have the condition.

Kass says previous research showed TGF-beta played a mixed role in various heart diseases, reducing arterial inflammation in some while harming valve and blood vessel function in others, such as people with Marfan syndrome. Until now, however, no explanation existed as to why any of these differences occurred, which cells controlled the TGF-beta signal, and which enzymes are stimulated as a result.

In the new study, researchers also found that in mice with hypertension-induced disease, blocking TGF-beta type 2 cell receptor stopped activities of another kind of regulating protein, called TGF-beta activated kinase (TAK-1). Its activation appears to play a key role in heart enlargement and in secreting proteins tied to scarring, as well as others tied to blood vessel formation.

Researchers began the study with injections of TGF-beta neutralizing antibodies to see if they could rein in heart-failing TGF-beta signaling. But the disease got worse in mice whose hearts had induced high blood pressure, and TGF-beta signaling persisted inside the muscle cells even though it was suppressed in other cells in the heart. The action of two other kinds of proteins closely tied to TGF-beta was similarly split, with the activity of Smad proteins suppressed only outside muscle cells, while TAK-1 production continued. This led Kass and his team to investigate what was happening differently inside muscle cells.

Subsequent testing in mice selectively bred to lack either one of the two TGF-beta receptors in the muscle cells revealed that blocking only the TGF-beta type 2 cell receptor shut down both Smad and TAK-1 activity, stalling enlargement and scarring. Blocking only the TGF-beta type 1 receptor,

however, failed to block TAK-1 activity, and disease-accelerating TGF-beta signaling persisted in non-muscle heart cells.

Researchers plan further tests in animals of chemicals that block TAK-1 as potential treatments for heart failure or other kinds of heart disease.

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