Three-way control of fetal heart-cell proliferation could help regenerate cardiac cells

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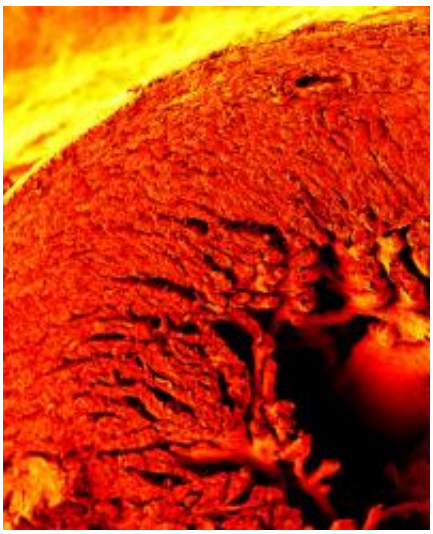

Thickened heart wall due to loss of Hdac2-Hopx function. Jon Epstein, MD, University of Pennsylvania School of Medicine

(PhysOrg.com) -- Heart muscle cells do not normally replicate in adult tissue, but multiply with abandoned during development. This is why the loss of heart muscle after a heart attack is so dire -- you can't grow enough new heart muscle to make up for the loss.

A team of researchers at the University of Pennsylvania School of Medicine describe the interconnections between three-molecules that

control fetal, heart-muscle-cell proliferation in a mouse model that will help cardiologists better understand the natural repair process after heart attacks and help scientists learn how to expand cardiac stem cells for regenerative therapies.

The research team, led by Jonathan Epstein, MD, chair of the Department of Cell and Developmental Biology, and Chinmay Trivedi, MD, PhD, an Instructor in the same department, report their findings in the cover article of the most recent issue of *Developmental Cell*.

The Penn team showed that an enzyme called Hdac2 directly modifies a protein called Gata4, and a third protein called Hopx, which appears to have adopted a new function. Hopx is a member of a family of ancient, evolutionally conserved proteins that normally bind DNA. In this case, however, rather than binding to DNA, it works to bring two other proteins, Hdac2 and Gata4, together. By performing this unexpected matchmaker function, Hopx helps to control the rate at which heart muscle cells divide.

“Although the degree to which hearts can repair themselves after injury is controversial, if there is a natural regeneration process, even if normally insufficient and modest, then approaches leveraging this insight this could be useful for boosting new growth so that it has a clinically significant effect,” says Epstein “We are eager to see if drugs like Hdac inhibitors will have this effect.”

The scientists found an unexpected function for Hdac2 as well. This enzyme normally acts as a switch that regulates how DNA is packaged inside the cell, and therefore how large groups of genes are turned on and off. Epstein said that his team was surprised discover that in the developing heart this packaging role was not the critical function.

“Rather, Hdac2 seems to be working directly on other proteins, and not

on DNA structure, to control replication of heart muscle cells," he says.

Hdac inhibitors are already in trials for cancer and one, valproic acid, has been used for decades to treat seizures. These inhibitors are a new class of agents that inhibit the proliferation of tumor cells in culture. Hdac inhibitors that are used to fight T cell lymphoma could possibly be used to enhance cardiac cell proliferation, say after a heart attack, when growing new heart muscle to replace damaged tissue would be is most needed.

"This could help to explain why Hdac inhibitors improve outcomes after heart attacks in animal models," says Trivedi.

Provided by University of Pennsylvania School of Medicine