

MARCH 24, 2010

Surprising New Clues on How to Build a Heart

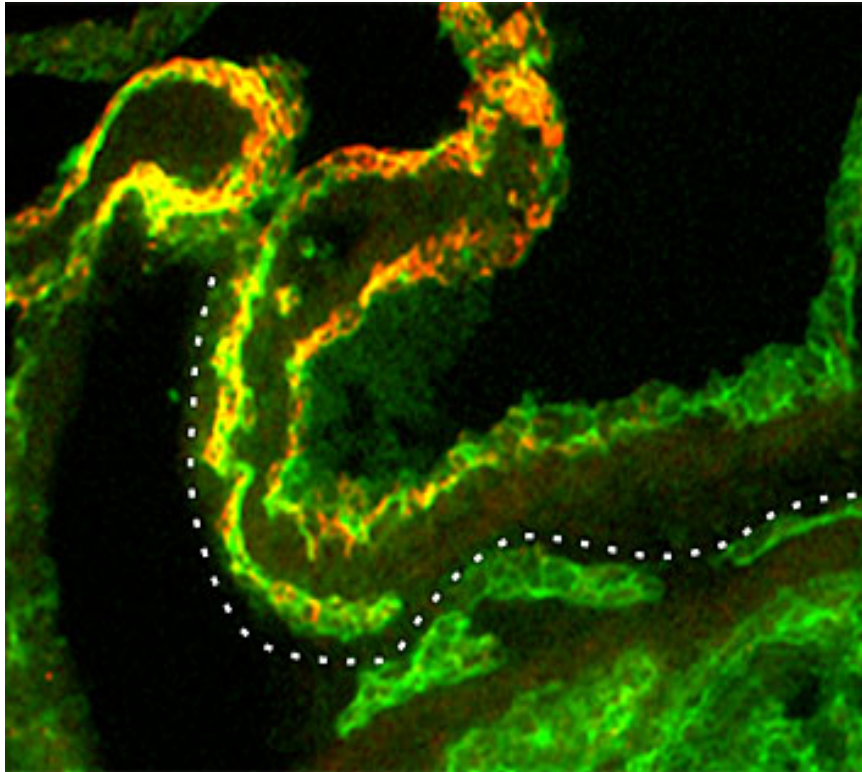


Image Title: In embryonic mice, gene expression changes in coronary vessel sprouts migrating on the heart from the vein (dotted line), reprogramming the cells so that they can form coronary arteries. The change in gene expression is seen as a shift from yellow to green fluorescence. - Kristy Red-Horse

Coronary artery disease is the leading cause of death worldwide, contributing to an estimated seven million deaths annually. Each year, tens of millions of people take medications or undergo surgery in hopes of staving off progression of the disease. But the surgical interventions – bypass grafts – are only a temporary fix. Sooner or later, they wear out.

Now, new studies of how the heart develops in growing mouse embryos have brought researchers a step closer to understanding how to induce the body's own cells to rebuild damaged coronary arteries.

The coronary arteries supply the heart with blood, enabling it to pump about 2,000 gallons of fluid throughout the body every day. When these arteries become blocked or otherwise damaged, portions of the heart can become starved for oxygen, leading to the pain of angina or to heart attacks.

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- Mark A. Krasnow

"Many coronary bypass grafts only last five to ten years and then people have to go back for another surgery," said Mark Krasnow, a Howard Hughes Medical Institute investigator at Stanford University. "If we can learn how to reprogram cells to build a new coronary artery just like the original, bypass grafts could last the rest of a lifetime."

The research, which was conducted largely by postdoctoral student Kristy Red-Horse in Krasnow's laboratory, is described in the March 25, 2010, issue of the journal *Nature*.

Krasnow's interest in coronary arteries grew out of his research into the development of the lungs and other branching tubular structures. "I've always been interested in the biological development of tubes," he said, "and the simplest and medically most important tube that could be grown outside the body is a coronary artery."

For more than a century, biologists have thought that coronary arteries form either from blood vessels that sprout from the aorta -- the main artery leading away from the heart -- or from a tissue called the proepicardium that covers the heart during development. But when Red-Horse carefully examined the hearts of mouse embryos, she found no evidence for either scenario.

"I looked at all the blood vessels in the heart during all stages of development," she said, "and saw vessels coming off the sinus venosus." The sinus venosus is the large vein that returns blood to the heart of a developing embryo. To her surprise, Red-Horse could find no evidence that vessels sprouted from the aorta or proepicardium. She then double-checked the observation by genetically marking cells in the sinus venosus and tracking their locations in developing mouse embryos and in tissue cultures. Many of the cells from the sinus venosus ended up in the coronary arteries and other blood vessels in the heart.

Further study showed that vessels branching from the sinus venosus migrate over the surface of the heart during development and invade the heart tissue. In the process, they convert from veins into more generalized blood vessels and then redifferentiate into arteries, capillaries, and new veins.

This developmental plasticity is one of the most intriguing aspects of the new research, according to Krasnow. "There is great interest in learning how to manipulate mature cells, turning them back to an earlier developmental stage or converting them to another type of cell for use in repairing damaged organs. This is a beautiful natural example of cells switching roles in response to chemical signals during development," he said. "And we suspect that other important blood vessels in the body form in a similar way -- by reprogramming venous cells. Now we're working to identify the signals that control these transitions."

Understanding how coronary arteries form could provide insights into how the arteries are damaged by disease. "Knowing what has gone wrong in the process might give us new ideas of how to arrest coronary artery disease," Krasnow said. Better understanding of the chemical signals involved in development also could make it possible to reinvigorate the growth of coronary arteries, either inside the body or outside the body for use in transplants.

"In the past, tissue engineering has been largely separate from developmental biology," said Krasnow. "But developmental biologists have been producing huge amounts of detailed information about how the body builds tubes, tissues, and organs. We're trying to move from understanding normal developmental programs to providing instructions to tissue engineers."