Coronary artery development mystery solved, may lead to better bypasses, Stanford study shows

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Scientists at the Stanford University School of Medicine studying cardiac development in mouse embryos have identified the source of cells that become the coronary arteries — the vessels that deliver blood to nourish the continuously pumping heart muscle. Surprisingly, the cells originate in an entirely different part of the heart than previously thought. Although they begin life as venous cells, directing blood into the chambers of the embryonic heart, they undergo a form of natural reprogramming as they migrate across and into the surface of the heart to become arteries and capillaries.

Understanding and recreating the conditions that allow these cells to switch identities from vein to artery could help the millions of people struggling with coronary artery disease, the scientists believe.

"Physicians performing coronary bypasses often use veins to reroute blood flow around clogged arteries," said biochemist and postdoctoral scholar Kristy Red-Horse, PhD. "But these veins fail more often and more quickly than transplanted arteries." Red-Horse is the lead author of the research, which will be published March 25 in *Nature*.

Few muscles in your body work as hard as your heart. Just like other muscles, the heart needs a reliable supply of oxygen. The coronary arteries encircle and burrow into the heart muscle to deliver fresh, oxygenated blood. Blocking the arteries, which occurs most commonly

when a deposit of plaque ruptures in the artery's lining, damages the heart muscle and can be fatal. It's also quite common: Coronary artery disease is the world's leading cause of death.

"If we can learn about how coronary arteries develop normally, we may be able to take that information and engineer better coronary bypass grafts, or even learn how to increase blood flow to the heart muscle without surgery," said professor and chair of biochemistry Mark Krasnow, MD, PhD. Krasnow is the senior author of the study and a Howard Hughes Medical Institute investigator.

Red-Horse began her study of heart development to solve a controversy. Anatomical studies of humans and other mammals had suggested the cells that make up the coronary arteries are derived from regions around the aorta. But more recent studies in chick embryos implicated an embryonic heart structure called the proepicardium.

When Red-Horse looked closely at the cells over time, however, she found that about 11.5 days after conception, cells from an embryonic cardiac structure called the sinus venosus, which directs blood into the developing heart, began to migrate across the surface of the muscle. By 14.5 days, they had become recognizable coronary arteries.

"This was really surprising," said Red-Horse. "I thought, as many others did, that these cells would arise from the proepicardium. The second surprise came when we realized the cells were de-differentiating from venous cells and becoming arteries."

While veins funnel deoxygenated blood back to the heart, arteries — coronary and otherwise — deliver fresh blood throughout the body. And although it might seem that a tube is a tube is a tube, with little to distinguish it other than its entry and exit points, the cells that make up veins and arteries are very different. Each has to handle a unique set of

conditions, including the pressure, flow patterns, pH and biochemical components of the blood they transport.

To confirm her finding, Red-Horse cultured developing hearts from mouse embryos in a dish. She found that, in contrast to controls, the chambers of hearts in which she had removed the sinus venosus kept beating but never developed coronary vessels.

Red-Horse then used a cell-marking technology developed by senior research scientist Hiroo Ueno, PhD, in the laboratory of Irving Weissman, MD, to label individual cells in the developing hearts of mouse embryos with different colors. The labeling experiments confirmed that a single cell from the sinus venosus could migrate across the heart and become not only the lining of the coronary arteries, but also of the veins and capillaries on the heart. Weissman is the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, and the Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research. Krasnow and Weissman are both members of the Stanford Cancer Center.

"This is a beautiful example of natural reprogramming," said Krasnow. "The heart is somehow telling these venous cells to leave the sinus venosus and convert into coronary arteries. If we can identify these molecular signals, we might be able to use them to construct coronary arteries for bypass surgery, which could be very important therapeutically."

Red-Horse and her colleagues are now trying to identify these signals and study how they change the cells' gene expression patterns as they undergo this conversion. The next step will be to see whether they can induce human cells to undergo a similar transformation.

"During the past several years, scientists have made great progress in

understanding how organs develop," said Krasnow. "And other scientists have made significant advances in tissue engineering and regenerative medicine. But the two groups don't talk to each other much. Now we're trying to apply what we've learned about how a body builds a vessel or an entire organ to building vessels and organs in the laboratory."

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