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Cardiac patches stimulate regeneration, improve function after heart attack

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When human hearts are injured, as during a heart attack, healthy tissue normally can't regrow. Researchers now demonstrate in rats that a sponge-like patch, soaked in a compound called periostin and placed over the injury, can not only get heart cells to begin dividing and making copies of themselves again, but also improves heart function. Their findings appear in the July 15 online edition of *Nature Medicine*.

Periostin is a component of the material that surrounds cells and is derived from the skin around bone. Though the mature heart only has tiny amounts, it's abundant during fetal heart development, and increased amounts are also made after skeletal-muscle injury, bone fracture and blood vessel injury, stimulating mature, specialized cells to begin dividing again. Led by Bernhard Kuhn, MD, in the Department of Cardiology at Children's Hospital Boston, the researchers theorized that placing periostin near the site of a myocardial infarction could help restore this growth-friendly environment and get heart tissue to regenerate.

Kuhn and colleagues at Massachusetts General Hospital and the Mount Sinai School of Medicine first stimulated mature, rod-shaped heart muscle cells (known as cardiomyocytes) with periostin in a Petri dish. About 1 percent of the cells entered the mitotic cell cycle – namely, they began dividing and replicating. (One percent seems like a small proportion, but normally the percentage is close to zero.)

"We found a small subpopulation of cells that could, with proper

stimulation, re-enter the cell cycle," says Kuhn, who was awarded the Young Investigator's Award for this research by the American College of Cardiology in March. "This finding supports the idea that differentiated cardiomyocytes can proliferate."

Using a small patch fashioned from a sponge-like material called Gelfoam, they then moved to experiments in rats with induced heart attacks. In half the rats, a patch that had been incubated with periostin was placed over the infarct site; the others received Gelfoam only.

Twelve weeks later, the treated patches were still releasing biologically-active periostin. The periostin-treated rats had improved cardiac pumping ability, as indicated by increased ejection fraction and improved ventricular remodeling on echocardiograms, and decreased left-ventricular wall stress on catheterization. They also had less scarring of heart tissue, a reduction in infarct size and a denser network of blood vessels feeding the area. In contrast, the rats receiving Gelfoam alone showed little if any improvement.

At the cellular level, the periostin-treated group had a 100-fold increase in the number of cardiomyocytes entering the cell cycle, and grew, on average, 6 million more cardiomyocytes, far exceeding the number of dying cells. (For perspective, the average rat heart has about 20 million cardiomyocytes overall.)

Kuhn, a pediatric cardiologist, envisions using a sustained-delivery periostin patch not only to treat adults with heart attack, but also to encourage cardiomyocyte proliferation in children with congenital heart disease.

"Many patients with severe congenital heart disease eventually hit a place where the heart isn't pumping adequately," Kuhn says. He envisions inserting the patch via a catheter, directly through the skin or

during heart surgery performed for other reasons.

“The most elegant approach would be systemic therapy – finding the most relevant parts of the periostin molecule and giving it by infusion,” he says.

Source: Children's Hospital Boston