Gel allows for targeted therapy after heart attack

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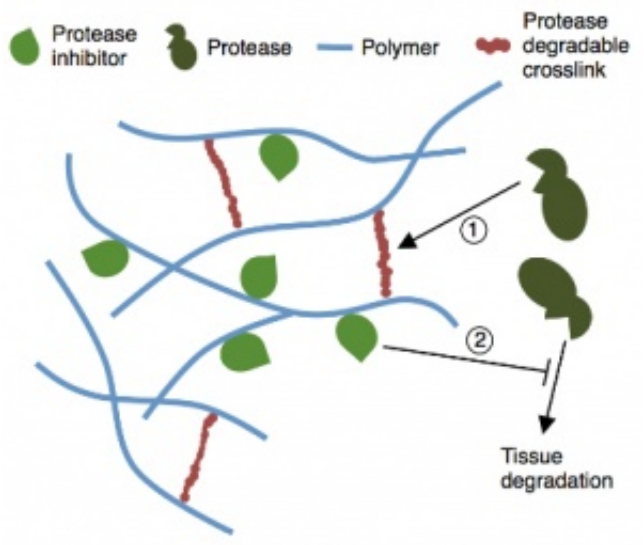

A schematic of the gel.

(Medical Xpress)—Combatting the tissue degrading enzymes that cause lasting damage following a heart attack is tricky. Each patient responds to a heart attack differently and damage can vary from one part of the heart muscle to another, but existing treatments can't be fine-tuned to deal with this variation.

University of Pennsylvania researchers have developed a way to address this problem via a material that can be applied directly to the damaged heart tissue. The potentially dangerous enzymes break down this gel-like

material, releasing enzyme inhibitors contained within. This responsive, balancing approach is ideal for keeping enzymes at the right level to minimize the long-term damage that can lead to congestive heart failure.

The ability of this gel to deliver enzyme inhibitors as needed suggests that the researchers' technique might also find use in other inflammation-related disorders, such as osteoarthritis where the same enzymes degrade cartilage tissue.

A study demonstrating their design's efficacy was published in the journal *Nature Materials*. It was led by Jason Burdick, professor of bioengineering in Penn's School of Engineering and Applied Science, and Brendan Purcell, a post-doctoral researcher in his lab. Joseph Gorman and Robert Gorman of the Department of Surgery in Penn's Perelman School of Medicine contributed to the research. The Penn team collaborated with Francis G. Spinale of the University of South Carolina School of Medicine, along with members of his research group.

"For heart attack patients, the first priority is restoring blood flow to the heart," Burdick said. "What's neglected, however, are the secondary effects that occur after a heart attack, including what's known as ventricular remodeling."

Remodeling is a phenomenon that ultimately changes the overall shape and performance of the heart. After a heart attack, the body naturally releases enzymes as part of the inflammatory response to injury. But when this response is sustained too long, those enzymes begin to break up the extracellular matrix inside the muscle tissue that makes up the walls of the heart, making it thinner and weaker. The walls balloon out under the pressure of normal heart pumping, resulting in an enlarged heart that pumps less blood with each beat.

Synthetic or lab-grown versions of inhibitors to the tissue-degrading

enzymes have been used in clinical trials, but only in a non-targeted fashion. Patients receive them intravenously or orally, with the hope that the inhibitor molecules make their way to the heart.

"As you can imagine, this type of delivery can lead to off-target problems," Burdick said. "In other tissues where enzymes and inhibitors are in balance, these extra inhibitors can throw that balance off. This can cause the stiffening of joints, for example."

"That's where our approach came in," Purcell said. "We used injectable gels to deliver the inhibitors locally, rather than systemically. And to really fine-tune the targeting, the innovation with this material is that it releases the inhibitor in response to the activity level of the enzyme."

The material the researchers used is known as a hydrogel, which in this design are squishy networks of sugars that are useful in mimicking different tissue environments. By making the hydrogel out of naturally occurring sugars, the researchers were able to hold the inhibitors within the hydrogel.

"We borrowed the way this specific inhibitor is localized and retained in normal tissues," Purcell said. "The inhibitors are physically held within the gel by electrostatic interactions with these sugars."

"If we didn't include this chemistry," Burdick said, "our experiments showed that about 80 percent of the inhibitor is released within a few days. When you have these bonds, only about 20 percent of the inhibitor is released over the course of a few weeks.

The researchers then selected the chemistry of cross-linking bonds that hold the hydrogel together so that the heart tissue-damaging enzyme could break them down. This was a key to the overall design of the gel. Absent the enzyme, the gel would prevent the inhibitor molecules from

escaping until they were needed.

"Once we add the enzymes, however, we can make the gel degrade away within a few hours, and we also showed that the level of enzyme correlates very nicely with how fast the gel degrades away and releases the inhibitor," Burdick said.

The researchers demonstrated this responsiveness in a petri dish, but also showed its potential for clinical effectiveness in an animal model. They used pigs, due to the anatomical similarity between porcine and human hearts.

"We used a microdialysis technique," Purcell said, "to show that, after a heart attack, local enzyme levels go way up, but when the inhibitor molecules are delivered via the gel, we see the activity level of this enzyme go down. Over the next 28 days, we also used imaging techniques to show thicker cardiac walls and less expansion and dilation of the ventricle. And, as a result, we see better performance in the heart using clinical measurements like ejection fraction, the amount of the blood the heart is pumping."

The study is part of an ongoing collaborative research effort between the Gorman Cardiovascular Research Group and the Burdick Biomaterials Laboratory, developing therapies intended to improve the heart's long-term response to a heart attack.

"While most groups working in this field are attempting to develop myocardial regenerative therapies, our team is focused on the biomechanical stabilization of the heart after heart attack," Robert Gorman said. "Most researchers working towards regenerative therapies often overlook an important fact, namely, that the overwhelming majority of patients who suffer heart attack initially have adequate heart function. We strongly believe that optimizing the function of the

surviving heart muscle after heart attack will be a more realistic and effective strategy than trying to regenerate the muscle that is lost."

"What's appealing about our approach," Burdick said, "is that we are trying to intervene early. We want to attenuate the remodeling process to limit these negative outcomes and prevent the onset of congestive heart failure."

The researchers are hopeful that these results will pave the way toward clinical use in human patients, where the gel would be applied to hearts via a catheter after the acute danger of a heart attack has passed.

More information: "Injectable and bioresponsive hydrogels for on-demand matrix metalloproteinase inhibition." Brendan P. Purcell, et al. *Nature Materials* (2014) DOI: 10.1038/nmat3922. Received 11 September 2013 Accepted 20 February 2014 Published online 30 March 2014

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