Simple chemical procedure augments therapeutic potential of stem cells

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Adult stem cells resemble couch potatoes if they hang out and divide in a dish for too long. They get fat and lose key surface proteins, which interferes with their movement and reduces their therapeutic potential. Now, via a simple chemical procedure, researchers have found a way to get these cells off the couch and over to their therapeutic target.

To do this, they simply added a molecule called SLeX to the surface of the cells. The procedure took just 45 minutes and restored an important biological function.

"Delivery remains one of the biggest hurdles to stem cell therapy," explains senior author Jeffrey Karp, an instructor at the Harvard-MIT Division of Health Sciences and Technology. "The blood stream offers a natural delivery vehicle, but stem cells don't move through blood vessels normally after being expanded in culture. Our procedure promises to overcome this obstacle."

These findings will be published online in the journal *Bioconjugate Chemistry* on Oct. 31.

In order for cells injected into the blood stream to be therapeutically useful, they need to take initiative to reach target tissues. But instead, cultured stem cells go with the flow. They move through the body quickly, carried by the current, which means they seldom contact the sides of blood vessels. Thus, they have fewer opportunities to escape into the surrounding tissue by squeezing between cells of the vessel wall.

Adult stem cells must escape before they can colonize surrounding tissue and rebuild damaged structures.

In February of 2008, HMS associate professor Robert Sackstein (at Brigham and Women's Hospital) and colleagues showed they could correct this problem by adding a particular molecule to the surface of adult stem cells. This molecule—a cousin of SLeX—formed temporary connections with proteins on the blood vessel wall, serving as a kind of weak tape. But Sackstein's method involved enzymes, which made the chemistry complicated. Karp's team achieved the same result without enzymes.

Karp lab postdoc Debanjan Sarkar simply flooded a dish of cells with three molecules—biotin, streptavidin, and SLeX—one after the other. The biotin and streptavidin anchored SLeX to the cell surface. Sarkar tweaked the concentrations of each molecule to maximize the cell's ability to roll along the interior of the blood vessel, rather than getting lost in the flow. He also confirmed that the altered cells were still viable.

"The method is very simple," says Sarkar, who is first author on the paper. "Plus, biotin and streptavidin work with many molecules, so labs can use this universal anchor we discovered to tackle other problems. They're not limited to sticking SLeX on cells."

The team worked with human cells extracted from the bone marrow. The cultures included mesenchymal stem cells (MSCs), which can form fat cells, cartilage, bone, tendon and ligaments, muscle cells, and even nerve cells. When injected into the bloodstream of patients, MSCs can home to the site of an injury and replace damaged tissue. But just a fraction of cultured MSCs currently reach their target in clinical trials. Karp's procedure might improve their homing abilities.

Karp cautions that his lab's discovery must be validated in animals,

before doctors can apply it in the clinic. He's collaborating with another lab to test the homing ability of the SLeX-dotted cells in mice.

"We need to confirm that this rolling behavior translates into increased homing and tissue repair," explains Karp. "We may need to tweak the cells further."

"This is definitely an approach that should be tried," adds Pamela Robey, chief of the Craniofacial and Skeletal Diseases Branch of the National Institute of Dental and Craniofacial Research. Robey is working to reconstruct three-dimensional tissues with MSCs. "Jeff hasn't tested the altered MSCs inside animals, and that's really the gold-standard, but his in vitro data looks promising."

Source: Harvard Medical School