Engineered cells could usher in programmable cell therapies

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In work that could jumpstart the promising field of cell therapy, in which cells are transplanted into the body to treat a variety of diseases and tissue defects, researchers at Brigham and Women's Hospital (BWH) have engineered cells that could solve one of the key challenges associated with the procedure: control of the cells and their microenvironment following transplantation.

In the work, reported in the journal *Biomaterials* on January 26, the team reports creating tiny internal depots within human mesenchymal adult stem cells, which among other functions are key to the generation of several tissues. These depots can slowly release a variety of agents to influence the behavior of not only the cells containing the depots, but also those close to them and even much farther away. The team demonstrated this by prompting mesenchymal stem cells to differentiate into the cells that make bone.

"This work could allow programmable cell therapies where the cell or the agent is the therapeutic," says Jeffrey Karp, leader of the work and co-director of the Center for Regenerative Therapeutics (ReGen Rx) at BWH. "For example, depots containing specific agents could enhance cell survival or expression of a particular growth factor. Cells could also be used as a delivery vehicle to shuttle drugs to target tissues that may be useful to accelerate tissue regeneration, or to deliver chemotherapeutics to tumors while minimizing systemic side effects."

Toward Cell Therapy

"Ten to fifteen years from now, people will visit cell infusion centers to receive routine therapy for multiple diseases and tissue defects," predicts Karp, who also holds appointments through Harvard Medical School, Harvard Stem Cell Institute, and the Harvard-MIT Division of Health Sciences and Technology (HST). For example, a person who has had a heart attack could be infused with cells that could help stimulate regeneration of new heart cells to replace those that have died and prevent eventual heart failure.

Today, however, there is only one cell therapy that has saved tens of thousands of lives: bone marrow transplantation. In this procedure healthy blood stem cells home in to the bone marrow to regenerate the blood system of cancer patients following bone marrow ablation through chemotherapy or radiation.

One of the reasons for the lack of success of other cell therapies is the inability to control the cells and the host's response following transplantation, says Karp. "We can exhibit exquisite control over cells in a [laboratory] dish—we can get them to do whatever we want. But when we transplant them into the body, their fate and function are at the mercy of the biological milieu. We typically lose complete control and this prevents us from achieving the promise of cell therapy."

There are ways to get around this problem, but they have limitations. For example, cells can be put on a scaffold or biomaterial that releases drugs or other agents that affect their behavior. The cells, however, have to stay in close proximity to the material to be impacted by the agents. Cells can also be genetically modified with viruses to produce agents that will influence their behavior, but this has potential safety concerns.

Natural Inspiration

The Karp team was inspired by the natural ability of many proteins and other agents to be transported in and out of cells. They already knew that cells could internalize the tiny synthetic particles used in the controlled delivery of drugs—could these particles be used in cell therapy?

To find out, the researchers developed biodegradable particles about ten times smaller than a mesenchymal stem cell (MSC). They loaded these particles with a dye, placed them near living MSCs, and found that the cells did indeed internalize them without immediately spitting them out. "Initially, this was a major challenge," comments James A. Ankrum, co-first author on the paper and an HST graduate student. "The particles needed to be small enough for the cells to internalize, yet large enough to prevent being shed by the cell." The dye was observed to seep from the tiny particle depots to the outside of the cell through the cell membrane over a period of several days.

Next, they replaced the dye with an agent known to spur MSCs to differentiate into osteoblasts, the cells that make bone. They found that not only did MSCs containing the depots differentiate into osteoblasts, but so did MSCs without depots that were nearby and even much further away. "We demonstrated that the fate of particle-carrying cells could be controlled, as well as the fates of neighboring and distant cells," says Debanjan Sarkar, co-first author of the paper and now a professor at the University of Buffalo.

Additional authors are Grace S. L. Teo of HST and Christopher V. Carman of Beth Israel Deaconess Hospital.

To date the team has demonstrated the engineered cells in laboratory systems designed to mimic the body. They are in the process of translating the work to animals. "If it works in vivo, it could have a

significant impact globally on cell therapy," says Karp, whose team has filed for a patent on the work.

Provided by Brigham and Women's Hospital