Medical Xpress

Team uses stem cell exosomes to induce damaged mouse hearts to self-repair

June 18 2015

A little more than a decade ago, researchers discovered that all cells secrete tiny communications modules jammed with an entire work crew of messages for other cells. Today, a team of researchers, led by stem cell researcher Raj Kishore, PhD, Director of the Stem Cell Therapy Program at the Center for Translational Medicine at Temple University School of Medicine (TUSM), is harnessing the communications vesicles excreted by stem cells and using them to induce the damaged heart to repair itself. Their research is the June 19 cover story in the leading cardiovascular research journal, *Circulation Research*.

"If your goal is to protect the heart, this is a pretty important finding," Dr. Kishore said. "You can robustly increase the heart's ability to repair itself without using the stem cells themselves. Our work shows a unique way to regenerate the heart using secreted vesicles from embryonic stem cells." The group is also beginning to determine which members of the "work crew" within the vesicles may be responsible for the damage repair.

The heart, for all its metronomic dependability, has little ability for self-repair. When heart muscle is damaged in a heart attack, the organ cannot replace the dead tissue and grow new. Instead, it must compensate for its lost pumping ability. That compensation comes with a high price: the heart grows large and flabby, and heart contraction weakens. Congestive heart failure ultimately contributes to, or causes one in nine deaths in the United States, and heart disease is the nation's leading killer.

From the start, heart damage seemed a problem custom-made for the burgeoning field of stem cell therapy. Researchers hoped that cells from embryos, or the rare stem cells harvested from adult tissue, could provide the heart with the ability to self-repair. Stem cells have unique properties. They are pluripotent—which means they can turn into any cell in the body. And they multiply continually. As knowledge about stem cells grew, several scientific teams conducted clinical trials on human heart attack victims, injecting damaged hearts with stem cells hoping the cells would take root and make new heart muscle. But results were disappointing, said Dr. Kishore, who is also a Professor of Pharmacology and Professor Medicine at TUSM. "People know if they inject hundreds of stem cells into an organ, you're going to be very lucky to find two of them the next day. They die. It's as though you're putting them into the fire and the fire burns them."

Another problem with pluripotent stem cells is the risk they pose. Because of their ability to turn into any cell, stem cells may create a kind of tumor called a teratoma, a mass of cells that can contain many different tissue types. Dr. Kishore arrived at an approach that avoided this risk after watching discoveries in cancer biology. Cancer researchers discovered that these tiny sacks excreted by cells, which were long thought to be involved with waste disposal, were actually more like a bottle carrying a set of messages. For instance, these extracellular vesicles proved to be one way a primary tumor communicated with distant metastases. Researchers renamed these vesicles exosomes and found that nearly all cell types excrete them. Dr. Kishore and his team began to study the exosomes of stem cells. Could these solve the heart-repair problem?

By 2011, Dr. Kishore's team published the first paper ever looking at stem cell exosomes and heart repair—making the team a pioneer in the field of exosomes and a trailblazer in the use of exosomes in heart disease. Even a year after that paper, exosome research remained in its

infancy with a total of 52 papers published on the subject. Today, there are 7,519 papers reporting on exosome research. Among those studies, only 13 or 14 look at exosomes in heart disease. This new paper by Dr. Kishore's team marks its third contribution to the science of exosomes and heart repair.

In the current study, Dr. Kishore's team used a mouse model of myocardial infarction—heart attack. Also involved in the research are Dr. Kishore's colleagues from Temple's Center for Translational Medicine, the Cardiovascular Research Center, and the Department of Pharmacology, as well as researchers from the Feinberg Cardiovascular Research Institute at Northwestern University in Chicago.

In the study, after infarct, mice received exosomes from either embryonic stem cells or exosomes from another type of cell called a fibroblast; mice receiving the fibroblast exosome served as the control group. The results were unmistakable. Mice that received exosomes from embryonic stem cells showed improved heart function after a heart attack compared to the control group. More heart muscle cells survived after infarct, and the heart exhibited less scar tissue. Fewer heart cells committed suicide—a process known as programmed cell death, or apoptosis. There was greater capillary development around the area of injury in the stem cell exosome group, which improved circulation and oxygen supply to the heart muscle. Further, there was a marked increase in cardiac progenitor cells—that is, the heart's own stem cells—and these survived and created new heart cells. The heartbeat was more powerful in the experimental group compared to the control group, and the kind of unhealthy enlargement that compensates for tissue damage was minimized.

The researchers then tested the effect of one of the most abundant gene-regulating molecules, or microRNAs, found in the stem cell exosome called miR-294. When miR-294 alone was introduced to cardiac stem

cells in the laboratory, it mimicked many of the effects seen when the entire exosome was delivered. "To a large extent, this micro-RNA alone can recapitulate the activity of the exosome," Dr. Kishore said. "But we can never say it is responsible for all of the response because embryonic stem cell exosomes have many other microRNAs."

Future research will look at both exosome therapy and the use of specific microRNAs for heart repair in the large animals and eventually in human trials.

"Our work shows that the best way to regenerate the heart is to augment the self-repair capabilities and increase the heart's own capacity to heal," Dr. Kishore said. "This way, we're avoiding risks associated with teratoma formation and other potential complications of using full stem cells. It's an exciting development in the field of heart disease."

Provided by Temple University

Citation: Team uses stem cell exosomes to induce damaged mouse hearts to self-repair (2015, June 18) retrieved 4 May 2024 from https://medicalxpress.com/news/2015-06-team-stem-cell-exosomes-mouse.html