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Stem cells in adult testes provide alternative to embryonic stem cells for organ regeneration

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Easily accessed and plentiful, adult stem cells found in a male patient's testicles might someday be used to create a wide range of tissue types to help him fight disease -- getting around the need for more controversial embryonic stem cells.

That's the promise of a breakthrough study in mice led by a team from Weill Cornell Medical College in New York City, who report their findings in the September 20 issue of *Nature*.

Using spermatogonial progenitor stem cells (SPCs) obtained from the mouse's testes, the researchers were able to redirect the cells' development in the lab to form so-called "multi-potent adult spermatogonial-derived stem cells" (MASCs).

It was these cells that went on to develop into working blood vessel (endothelial) cells and tissue, as well as cardiac cells, brain cells and a host of other cell types.

Prior research conducted elsewhere has used genetic manipulation to reprogram adult cells derived from connective tissue to acquire stem-cell potential, differentiating into various organ-specific tissues. However, this reprogramming method -- called "induced pluripotency" -- resulted in generation of multi-potent stem cells that carried an increased risk of transforming into malignant cells.

"What's really novel about our work is that -- unlike induced pluripotency -- these mouse SPCs do not require any addition or tweaking of genes to get them to form the multi-potent cells (MASCs) that then go on to produce all of these cell types," notes senior author Dr. Shahin Rafii, Arthur Belfer Professor of Genetic Medicine and director of the Ansary Stem Cell Center for Regenerative Medicine at Weill Cornell Medical College and a noted Howard Hughes Medical Institute investigator.

"Some hurdles remain, of course -- we have to replicate these findings in humans, and we haven't discovered the exact 'switch' that would allow us to control SPC development on demand," Dr. Rafii says. "Nevertheless, it appears that these unique specialized spermatogonial cells could be an easily obtained and manipulated source of stem cells with exactly the same capability to form new tissues that we see in embryonic stem cells."

SPCs lie within a specific area of the testes and their sole function is to generate the precursors to sperm. "Normally, the spermatogonial progenitor cell is committed to only that function, and they're remarkably efficient, keeping men fertile well into advanced age," notes the study's lead author, Dr. Marco Seandel, researcher at the Howard Hughes Medical Institute and researcher/medical oncology fellow at Memorial Sloan-Kettering Cancer Center in New York City. Dr. Seandel provided the first real breakthrough in this research, developing the first efficient means of growing large quantities of SPCs for experimental use in the lab.

"That really allowed us to go full steam ahead in examining the potential of these very interesting cells," explains Dr. Rafii.

In their experiments, the Weill Cornell team concocted the perfect in vitro biochemical environment for the SPCs. This included particular

helper cell types and growth factors aimed at fostering SPCs development away from creating germ cells and towards what scientists called "multipotency" -- the ability to develop into many different cell types.

Along the way, the team also cleared another hurdle.

"One problem with working with SPCs is that they've been extremely difficult to identify. We discovered that, within the testicular environment, only SPCs express a particular marker called GPR125," Dr. Seandel says. "That's a quantum leap forward in terms of being able to harvest and work with these cells."

Left to "soak" in their specially designed cell culture conditions, SPCs eventually made the change the team was hoping for. They did not develop into germ cells but instead grew to become multi-potent adult spermatogonial-derived stem cells (MASCs).

In both in vitro and mouse-tissue studies, the Weill Cornell group watched as the MASCs differentiated into the full range of cell types.

"We took them furthest when it came to endothelial cells," says Dr. Daylon James, a co-author and investigator in Dr. Rafii's laboratory. "In experiments in live mouse tissue, we were able to show that these MASC-derived endothelial cells did more than just form -- they also joined up with, and functioned alongside, other blood vessels."

MASCs also produced contractile "beating heart" cardiac cells, neurons, and muscle cells in the laboratory, the researchers add.

But challenges remain. "We still don't understand the exact biochemical and genetic 'switch' that tells the cells to become MASCs," Dr. Seandel says. "Discovering that switch will be crucial to our being able to create

MASCs on a routine basis."

"The other hurdle is to repeat this success in human cells, by utilizing the same stem-cell markers, including GPR125 and also another specific marker, Plzf," states Dr. Pier Paolo Pandolfi, a collaborator in the study. Dr. Pandolfi is currently a professor at Harvard Medical School. Drs. Ilaria Falciatori, Sergey Shmelkov and Jiyeon Kim are other researchers in Dr. Rafii's lab, who are using GPR125 to isolate stem cells from other adult tissues with the potential of converting them into multi-potent stem cells with regenerative potential.

Still, the findings in Nature are extremely promising.

"For male patients, it could someday mean a readily available source of stem cells that gets around ethical issues linked to embryonic stem cells. It also avoids issues linked to tissue transplant rejection, since these 'autologous stem cells' are derived from the patient's own body," Dr. Rafii says. Given the pioneering surgical technology developed by the Department of Urology at Weill Cornell -- by Drs. Peter Schlegel, Marc Goldstein and Douglas Scherr -- it is expected that routine retrieval of adult human testicular tissue could be performed safely and in a timely fashion.

Would such an approach work in the female ovary, which also contains a large population of germ cells" The Weill Cornell team says similar techniques might work there as well, although at this point it's just a theory.

"Our achievement using these testes-derived cells has taken us over a decade of painstaking investigation to achieve," says Dr. Rafii. "It points to the potential of this remarkable, but -- until now -- poorly accessed and understood stem cell."

"We hope this seminal paper will set the stage for designing clinical strategies for regenerating failing organs in patients with heart disease, Alzheimer's, Parkinson's, stroke, diabetes, arthritis, macular degeneration and infertility induced by chemotherapy and irradiation," Dr. Rafii adds. "Delivering stem cells derived from MASCs, loaded with toxic factors, to the tumor microenvironment may also provide a novel strategy to target tumor blood vessels and inhibit cancer growth and metastasis."

Source: New York- Presbyterian Hospital