

Researchers create genetically matched embryonic stem cells for transplantation

December 14 2006

Researchers at Children's Hospital Boston report a new and efficient strategy, using eggs alone, for creating mouse embryonic stem cells that can be transplanted without the risk of rejection because the cells are compatible with the recipient's immune system. The findings will be published online in the journal *Science* on December 14.

Though done in mice, the work establishes the principle of using unfertilized eggs as a source of customized embryonic stem cells that are genetically matched to the egg donor at the genes that control recognition of cells by the immune system, making them potentially useful for transplantation therapies. There are several caveats, including the fact that only females could benefit from this technique, donating their own eggs to generate the stem cells, and concerns that the tissues derived from this special type of embryonic stem cells might not function normally.

"This technique, if proven effective in humans, offers an efficient way of generating customized stem cell lines from women," says George Q. Daley, MD, PhD, senior author on the paper, who is the Associate Director of the Children's Hospital Boston Stem Cell Program and a member of the Executive Committee of the Harvard Stem Cell Institute. "It would eliminate tissue matching and tissue rejection problems, a major obstacle to successful tissue transplantation."

Embryonic stem cells are "master cells" that can generate all tissue types in the body. In 2002, Daley's laboratory collaborated with the laboratory



of Rudolf Jaenisch, PhD, of the Whitehead Institute, MIT to demonstrate the first use of another method, somatic cell nuclear transfer, to create customized embryonic stem cells to repair genetic defects in mice. But somatic cell nuclear transfer (sometimes called therapeutic cloning) is a technically demanding and inefficient process that involves transferring the nucleus of a donor cell into an egg from which the nucleus has been removed.

"We will not stop testing nuclear transfer, because it is the only means we know for generating embryonic stem cells that are genetically identical to a patient," says Daley, who heads one of two Harvard Stem Cell Institute-associated labs attempting to create human embryonic stem cells with that technique. "However, generating embryonic stem cells from unfertilized eggs is far more efficient than nuclear transfer, and therefore may allow us to move toward human applications sooner."

In the new study, Daley, first author Kitai Kim, PhD, and colleagues at Harvard Medical School, Brigham and Women's Hospital and Massachusetts General Hospital used unfertilized eggs of mice to create so-called parthenogenetic embryonic stem cells. Parthenogenesis is a method of reproduction, common in plants and in some animals, in which the female can generate offspring without the contribution of a male. It doesn't normally occur in mice, but Daley, Kim and colleagues were able to induce unfertilized mouse eggs to develop through a series of chemical treatments, then generated embryonic stem cells.

Next, they used genetic typing to identify those embryonic stem cells that shared with the egg donor the genes responsible for tissue matching, called the major histocompatibility complex (MHC). When they injected these selected embryonic stem cells into MHC-matched mice, a variety of specialized tissues formed, with no rejection and no need to suppress the recipients' immune system.



Daley's laboratory at Children's Hospital Boston is now trying to replicate its results with human eggs.

As Daley noted, there are several potential limitations to embryonic stem cells generated by parthenogenesis. First, since parthenogenetic embryonic stem cells are made from eggs, the technique is only applicable to females. (Methods exist for deriving embryonic stem cells using sperm from men, but these techniques are as technically challenging and inefficient as somatic cell nuclear transfer, Daley says.)

There are also potential safety concerns. Embryonic stem cells created through parthenogenesis have altered expression of certain genes that are "imprinted." Imprinted genes are marked for expression in a special way based on whether they are passed to offspring by the egg or the sperm. Because parthenogenetic embryonic stem cells are made from eggs only, they carry no paternally imprinted genes, and instead carry two copies of maternally imprinted genes. Altered expression of imprinted genes has been linked with cancer and poor growth in some tissues. In addition, embryonic stem cells created through parthenogenesis may have some regions of their genome that contain duplicated copies of mutant genes that have been linked with malignancies or abnormal tissue growth.

"Right now this technique is useful for basic research, but we are hopeful that parthenogenetic cells might prove useful for therapies," Daley says. "Our cells produce normal tissues in mice, and there is a report in the clinical literature of a human patient whose blood was derived entirely from parthenogenetic cells. However, we'll have to demonstrate the safety and durability of cells derived from parthenogenetic embryonic stem cells before we could imagine any clinical use."

Source: Children's Hospital Boston



Citation: Researchers create genetically matched embryonic stem cells for transplantation (2006, December 14) retrieved 5 May 2024 from <u>https://medicalxpress.com/news/2006-12-genetically-embryonic-stem-cells-transplantation.html</u>

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