Discredited Korean embryonic stem cells' true origins revealed

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A report from researchers at Children's Hospital Boston and the Harvard Stem Cell Institute sheds new light on a now-discredited Korean embryonic stem cell line, setting the historical record straight and also establishing a much-needed set of standards for characterizing human embryonic stem cells. The report was published online August 2 by the journal *Cell Stem Cell*.

In 2004, Korean investigators announced the creation of the world's first human embryonic stem cells through somatic cell nuclear transfer, entailing transfer of genetic material from a cell in the body into an egg. Now, research led by Kitai Kim, PhD, and George Q. Daley, MD, PhD, of the Children's Hospital Boston Stem Cell Program demonstrates that the Koreans unwittingly created something entirely different – the world's first human embryonic stem cell to be derived by parthenogenesis, a process that creates an embryo containing genetic material only from the donor egg.

"We know now that the Koreans' first supposed nuclear transfer-derived stem cell line was actually derived from the woman's egg alone," Daley says.

The Koreans' 2004 paper, published in Science, was retracted by the journal in early 2006 amid evidence that researchers Hwang Woo-Suk et al. had falsified their data. An initial investigation of the Korean group's first embryonic stem cell line suggested it might be parthenogenetic in origin, but the analysis was inconclusive, and the cells' origin, until now,

had never been fully explained in a peer-reviewed journal.

Kim, Daley and collaborators used sophisticated genetic techniques to compare mouse embryonic stem cells derived from different sources: from embryos produced by natural fertilization; from embryos produced by parthenogenesis (through artificial activation of unfertilized eggs); and from embryos created through somatic cell nuclear transfer (replacing the nucleus of an egg with the nucleus from a cell in the body). They also tested three human embryonic stem cells isolated from fertilized embryos as well as the Korean line of human cells claimed to have been created through nuclear transfer.

They discovered that parthenogenetic embryonic stem cells have a distinct genetic signature that reflects their biological origins. All cells typically contain paired sets of chromosomes, one inherited from the mother and the other from the father. During the process of parthenogenesis, one set of chromosomes is duplicated, resulting in both chromosomes of the pair being of one parental type or the other (a pattern called homozygosity, which has reduced genetic diversity). Kim and Daley showed previously that because chromosomes often exchange genetic material early in the process of cell division that creates the egg (meiosis), the duplicated chromosomes are not actually identical, but have places where the genes differ between members of the pair (called heterozygosity). In embryonic stem cells of parthenogenetic origin, this occurs especially toward the ends of the chromosomes, which are more likely to exchange genetic material, rather than the middle. In contrast, embryonic stem cells created through nuclear transfer show a consistent pattern of variation through all regions of the chromosome -- thus making them easily distinguishable from parthenogenetic cells.

The Korean cell line displays a genetic pattern that is clearly consistent with a parthenogenetic origin, Kim and Daley now show.

Because mistakes during nuclear transfer can result in parthenogenetic cells, Daley believes that the Hwang group generated parthenogenetic stem cells by accident, and didn't have the tools to conclusively determine what they had created. The first isolation of parthenogenetic stem cells from humans would have been an important contribution, but the Hwang group's attempt to pass off the cells as made by nuclear transfer was instead "a woeful case of misconduct," he says.

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. Daley's group has been stimulating parthenogenesis in the laboratory as a way of creating customized embryonic stem cells that can treat disease without being rejected by the immune system.

The team recently demonstrated in mice a feasible technique for generating parthenogenetic embryonic stem cells that were genetically matched to the egg donor at the genes that control tissue typing, and are attempting to create similar cells from humans.

Daley, who is a member of the executive committee of the Harvard Stem Cell Institute and president of the International Society for Stem Cell Research, notes that scientists now have two powerful tools: human parthenogenesis, which appears to be an efficient means of producing human embryonic stem cells, and genetic screening, which can be used to scan stem cells and help define their origins.

Daley imagines a future in which scientists could create a master bank of parthenogenetic embryonic stem cells with genetically selected cells that could be matched to patients on the genes that control immune rejection. Having all the genetic material come from the mother, as it does in parthenogenesis, reduces tissue compatibility issues.

"There has been an advance in the idea that you can couple parthenogenesis and genetic screening to identify those cell lines that are going to be most helpful," Daley says.

Parthenogenetic embryonic stem cells do not obviate the need to also create embryonic stem cells through nuclear transfer or from human embryos, he adds. "Each of the strategies has its own applications, and there are certain types of research and certain fundamental questions—and major areas of therapy—that can only be accomplished with these other types of stem cells," Daley says.

Source: Children's Hospital Boston