Scientists identify a mouse embryonic stem cell more like our own

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Scientists have discovered a new type of mouse embryonic stem cell that is the closest counterpart yet to human embryonic stem (ES) cells, the National Institutes of Health (NIH) announced today. The cells are expected to serve as an improved model for human ES cells in studies of regeneration, disease pathology and basic stem cell biology.

The findings, reported on-line today in Nature, are the result of a collaborative effort among scientists at the National Institute of Neurological Disorders and Stroke (NINDS), the National Cancer Institute (NCI) – both part of NIH – and the University of Oxford, U.K.

"These mouse cells will teach us about how human embryonic stem cells generate the hundreds of cell types that make up the human body – knowledge that will help us realize the promise of stem cell therapy," said NIH Director Elias A. Zerhouni, M.D.

Compared to traditionally studied mouse ES cells, the new cells – called epiblast stem cells – are not only a closer match to human ES cells, they are one step farther down the developmental path toward the cell types of the adult mouse. They appear at a later stage of development when the embryo and supportive tissues have become more defined.

"You can view this cell as the beginning of the organism," said lead scientist Ronald McKay, Ph.D., a senior investigator at NINDS. Dr. McKay also directs the NIH Stem Cell Unit, responsible for storing and characterizing human ES cells approved for use in federally funded

research.

Mouse ES cells are typically used as a proxy for human ES cells, even though they differ in several ways, from their appearance under a microscope to chemical modifications in their DNA. By these measures and others, the epiblast stem cells isolated by Dr. McKay and his team are a closer match to human ES cells. Moreover, because they're farther along the developmental timeline than the traditionally studied cells, they could offer scientists a unique glimpse at a critical point in the life of an ES cell – a time when it is poised to start producing mature cell types, including neurons, muscle and bone.

One key to isolating the epiblast stem cells was to work with slightly older mouse embryos. Traditionally studied mouse ES cells come from embryos that haven't yet implanted themselves in the uterine wall. The epiblast is a cluster of cells that forms after implantation. In mammals, it will give rise to all the cells that make up the adult animal, while surrounding tissues will become supportive structures like the placenta.

Another key was to grow the mouse cells using methods developed for growing human ES cells, an innovation made by Paul Tesar, a graduate student in the NIH-Oxford Biomedical Research Scholars program. The program has allowed Mr. Tesar to split his time between the two institutions; it also provided a link between Dr. McKay and Professor Sir Richard Gardner, an expert on mouse embryonic development at Oxford.

Mr. Tesar and Josh Chenoweth, Ph.D., a postdoctoral fellow at NINDS, did the bulk of the work comparing the epiblast stem cells to established mouse and human ES cell lines.

First, they tested whether the epiblast stem cells are capable of becoming diverse cell types – a defining feature of ES cells. The epiblast stem cells

passed two such tests. When grown in test tubes, the cells also morphed – or differentiated – into neuron-like cells, muscle cells, and cells found in the body's inner organs, depending on the growth medium. When injected into immunodeficient mice, they formed teratomas – large tumors containing bits of cartilage, muscle, fat, skin and other tissues. David Mack, Ph.D., a postdoctoral fellow at NCI, assisted with the teratoma experiments.

Other experiments revealed how similar the epiblast stem cells are to human ES cells, and how different those two cell types are from the classic mouse ES cell. For instance, human ES cells and mouse epiblast stem cells possess nearly the same set of active transcription factors – proteins that turn genes on and off. They also have similar chemical tags on their DNA, making it more or less receptive to transcription factors. And in the process of deciding whether they will become gametes (sperm and egg cells) or somatic cells (everything else), epiblast stem cells seem farther along than the classic mouse ES cells. In mouse ES cells, some genes associated with the gamete lineage are turned on. In human ES and mouse epiblast stem cells, those genes are off, but can be switched on through exposure to growth factors.

The similarities between the two cell types, along with the discovery that the same methods can be used to rear them, show that their growth and differentiation are regulated in the same way, Dr. McKay said.

"Understanding what stem cells are and how they grow in a dish are still central problems in medical research," he said. "If we know how to control their growth and differentiation, we can regenerate cells lost to injury or disease."

With such knowledge, for example, adult human cells could be reprogrammed to act more like human ES cells. One lab recently coaxed mouse skin cells to behave like classic mouse ES cells; the new mouse

epiblast cell could be the key to extending this same trick to human tissue.

Dr. McKay emphasized that despite their importance, the new cells won't render the classic mouse ES cells obsolete. The classic cells are easier to grow and are the primary tool that researchers use to create mouse models of human genetic diseases.

Source: National Institute of Neurological Disorders and Stroke