Understanding the beginnings of embryonic stem cells helps predict the future

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Ordinarily, embryonic stem cells exist only a day or two as they begin the formation of the embryo itself. Then they are gone.

In the laboratory dish, however, they act more like perpetual stem cells – renewing themselves and exhibiting the ability to form cells of almost any type, a status called totipotency.

Dr. Thomas Zwaka, associate professor in the Stem Cell and Regenerative Medicine Center at Baylor College of Medicine, and his colleagues here and abroad showed that laboratory-grown cells express a protein called Blimp1, which represses differentiation to somatic or regular tissue cells during germ cell development. Studies of these cells show that they also express other genes associated with early germ cell specification. A report on their work published online today in the journal *Current Biology*. It will appear in the October 25 print edition of the journal.

"What are embryonic stem cells?" said Zwaka, who is also part of the Center for Cell and Gene Therapy at BCM, Texas Children's Hospital and The Methodist Hospital. "It is quite a surprise that we have them. In the embryo, there is a mass of cells that eventually form the embryo, but they do not persist. They do not have a program built in that allows them to persist."

To study this, he examined mice. If you put the mass of cells in a Petri dish in the laboratory, they act as thought they are stem cells with the

ability for self renewal and totipotency – the ability to become almost any kind of cell.

Understanding what happens early in development of embryonic stem cells in the laboratory might help make the process of growing them and another, new kind of stem cell called induced pluripotent stem cells – cells with the potential of becoming many different kinds of tissues that are derived from somatic or adult cells.

"These induced pluripotent stem cells are poorly understood," said Zwaka. "If we know what is happening when we derive embryonic stem cells in the laboratory, it will inform us when we make induced pluripotent stem cells. The end product is similar."

The process of making the induced pluripotent stem cells is noisy and random, he said.

"Every time, the clones look different and emerge at different time points," said Zwaka. By contrast, embryonic development is like clockwork, with events occurring at the same point with each embryo. However, development of embryonic stem cells in the laboratory becomes more disorganized as time goes on.

In the laboratory dish, the mouse embryo continues to develop at a fairly organized rate for two or three days, but when the single cells are separated and grown singly, the embryonic stem cells begin to emerge. Only a tiny subset – roughly 1 percent – of the cells become an embryonic stem cell in the laboratory."

"We found that these cells (from the embryonic stem cells come) resemble in almost every feature an early germ cell (primordial germ cell)," he said. (Primordial germ cells are the source of gametes – eggs and sperm.)

"It seems that these seeming germ cells are the cells that make the embryonic stem cells in culture," he said.

"Germ cells in the embryo are unique and pluripotent (able to become many different kinds of cells) and have a very sophisticated program in them that protects the from becoming somatic cells (specific tissue cells)," he said. "They retain their primitive state." Blimp1 is a master regulator of germ cells.

In the future, he said, he hopes that investigators in both fields can collaborate and learn from one another.

Provided by Baylor College of Medicine