

U-M team identifies gene that regulates blood-forming fetal stem cells

In the rancorous public debate over federal research funding, stem cells are generally assigned to one of two categories: embryonic or adult. But that's a false dichotomy and an oversimplification. A new University of Michigan study adds to mounting evidence that stem cells in the developing fetus are distinct from both embryonic and adult stem cells.

In the last several years, stem cell researchers have realized that fetal stem cells comprise a separate class. They recognized, for example, that fetal blood-forming stem cells in umbilical cord blood behave differently than adult blood-forming stem cells after transplantation into patients.

Now a U-M team led by Sean Morrison has identified the first known gene, Sox17, required for the maintenance of blood-forming stem cells in fetal mice, but not in adult mice. The discovery provides a critical insight into the mechanisms that distinguish fetal blood-forming stem cells from their adult counterparts.

The findings could also lead to a deeper understanding of diseases such as childhood leukemias, said Morrison, director of the U-M Center for Stem Cell Biology and a Howard Hughes Medical Institute investigator. Childhood leukemias are cancers that afflict blood-forming cells and hijack normal stem cell self-renewal mechanisms.

"One of the next questions in our cross hairs is whether Sox17 gets inappropriately activated in certain childhood leukemias---and that's an idea that nobody had in their mind before this work," Morrison said. "If it's true, it'll give us a new target for cancer."

The Sox17 results will be published online July 26 in the journal Cell. U-M's Injune Kim is lead author of the paper; Morrison and U-M's Thomas Saunders are co-authors.

"Identification of Sox17 could also facilitate efforts to form blood-forming stem cells from human embryonic stem cells, a goal that could enhance bone marrow transplantation," Kim said.

The Sox 17 study is part of a larger, ongoing U-M effort to understand how stem cells are regulated at different stages of life. Last September, Morrison's team reported that old stem cells don't simply wear out; a gene called Ink4a actively shuts them down.

"Each time we identify one of these genes, we get a new insight into what stem cells really are, what regulates their identity and how their age-specific functions work," Morrison said. That information could lead to new treatments for degenerative diseases.

Stem cells generate all of the tissues in the developing human body and later in life provide replacement cells when adult tissues are damaged or wear out. Stem cells that form blood and immune-system cells are called hematopoietic stem cells.

In the latest study, Kim and Morrison looked for genes required to maintain hematopoietic stem cells in fetal mice, but not in adult mice. They found that Sox17 was turned on in fetal and neonatal hematopoietic stem cells but not adult hematopoietic stem cells.

To test whether Sox17 was functionally important for fetal and neonatal blood-forming stem cells, the researchers deleted the Sox17 gene in laboratory mice. This led to the loss of fetal and neonatal, but not adult, hematopoietic stem cells.

In follow-up experiments, mice were irradiated to destroy their blood-forming stem cells. Then replacement fetal or neonatal blood-forming cells were transplanted into the mice---some containing the Sox17 gene and others lacking it. The mice that received Sox17-bearing cells were able to regenerate their blood systems. Those that received cells lacking Sox17 could not.

"Sox17 is really a critical player," Morrison said. "If you knock it out in mice, they never develop a blood system. They never form blood cells."

Source: University of Michigan

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