Stem cells' 'suspended' state preserved by key step, scientists report

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Scientists have identified a gene that is essential for embryonic stem cells to maintain their all-purpose, pluripotent state. Exploiting the finding may lead to a greater understanding of how cells acquire their specialized states and provide a strategy to efficiently reprogram mature cells back into the pluripotent state, an elusive step in stem cell research but one crucial to a range of potential clinical treatments.

The research was led by University of California, San Francisco scientists. It is being reported Wednesday, July 8, 2009, in the advanced online edition of the journal *Nature*, and will be published in the journal's print edition at the end of July.

Embryonic stem cells are suspended in an "open" state, uniquely poised to become any one of many types of specialized cells, as genetic instructions dictate. Directing the specialization of embryonic stem cells to cells needed by patients is an area of enormous promise in stem cell research. Reversing the natural process -- converting specialized cells back into the all-purpose stem cell stage - is another great promise of stem cell research.

Reprogramming specialized cells from Parkinson's patients, for example, would allow scientists to study the mechanisms that cause neurons in the brain to develop the disease. It also could lead to treatments by directing the restored stem cells to produce healthy neurons to introduce into patients.

The new research, conducted on mouse embryo cells, revealed that a gene known as Chd1 loosens the packaging that normally protects DNA in the cell nucleus. This step, known as chromatin remodeling, allows the cell's protein-making machinery to gain access to the DNA and transform progenitor cells into specialized cells and tissue, such as neurons, muscle and bone.

A number of genes are known to trigger chromatin remodeling, allowing small sections of DNA to become accessible in order to make specific proteins. Chd1 is the first gene found to regulate a "global" loosening of the DNA in embryonic stem cells, the scientists report. The global condition sets the stage for turning on many different genes to make a broad range of specialized cells.

"Embryonic stem cells are characterized by this open state, but, up to now, we didn't know the mechanisms that maintain this state, or even if it is necessary for the full stem cell potential," said Alexandre Gaspar-Maia, lead author of the paper.

"We found that Chd1 is critical for both, and for allowing an efficient reprogramming. Chd1 is important for allowing the normal differentiation process, and it is essential for playing the 'differentiation tape' backwards - bringing differentiated cells back to pluripotency."

Gaspar-Maia is a graduate student (from the PhD Program in Experimental Biology and Biomedicine, at the University of Coimbra, Portugal) in the lab of senior author Miguel Ramalho-Santos, PhD, of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF.

The scientists discovered the pivotal role of Chd1 by using the powerful technique of RNA interference, or RNAi, to screen this gene and 40 other candidate genes. (RNAi is a naturally occurring process in which

small RNAs bind to other RNAs to increase or decrease their activity.) In this case, the scientists used the technique to silence Chd1. When they did so, embryonic stem cells could not make the full range of specialized cells.

In a laboratory test used to simulate normal cell specialization, the scientists detected no differentiation of cardiac muscle, and also no formation of a tissue known as primitive endoderm, which is essential for the embryo to survive and develop.

Chd1 also was shown by the research team to be necessary for the reprogramming of specialized cells back to the pluripotent stem cell state. The team plans to study chromatin remodeling in still more detail to clarify what other molecules work in concert with the Chd1 gene to direct the process. This would aid efforts to increase the efficiency and safety of reprogramming cells. This research may also shed light on how cells transition from one type to another, a process that happens normally during embryonic development and goes astray in cancer.

"We now know that Chd1 is essential, and, so far, appears unique in its global effect, but we expect that there are major players yet to be discovered," said senior author Ramalho-Santos, UCSF assistant professor of obstetrics, gynecology and reproductive sciences, and pathology.

"If we can understand how Chd1 works, that will also tell us more about how the cells regulate their precise specialization during development, and turn on their pluripotency program during reprogramming."

The scientists conclude that embryonic stem cells exist in a dynamic state, poised between the open condition that may assure the cell's full potential, and the more constrained state that allows only certain kinds of cells to progress. Chd1, they say, is central to maintaining the open,

pluripotent stem cell state.

More information: www.nature.com/nature/journal/ … abs/nature08212.html

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