Cell biologists discover on-off switch for key stem cell gene

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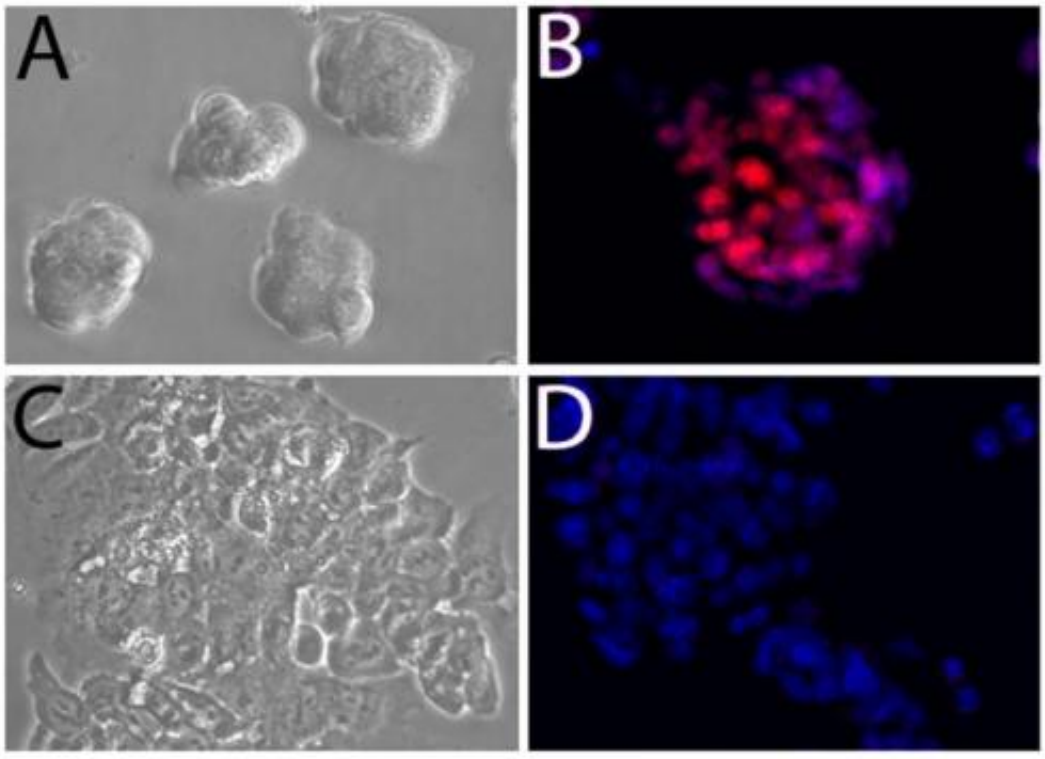

These are images of mouse embryonic stem cells which grow in a round colony of cells (A) and express Sox2 (B), shown in red. Sox2 control region-deleted cells have lost the typical appearance of embryonic stem cells (C) and do not express Sox2 (D). The DNA is shown in blue in B and D. Credit: Jennifer Mitchell/University of Toronto

Consider the relationship between an air traffic controller and a pilot. The pilot gets the passengers to their destination, but the air traffic

controller decides when the plane can take off and when it must wait. The same relationship plays out at the cellular level in animals, including humans. A region of an animal's genome - the controller - directs when a particular gene - the pilot - can perform its prescribed function.

A new study by cell and systems biologists at the University of Toronto (U of T) investigating stem cells in mice shows, for the first time, an instance of such a relationship between the Sox2 gene which is critical for early development, and a region elsewhere on the genome that effectively regulates its activity. The discovery could mean a significant advance in the emerging field of human regenerative medicine, as the Sox2 gene is essential for maintaining embryonic stem cells that can develop into any cell type of a mature animal.

"We studied how the Sox2 gene is turned on in mice, and found the region of the genome that is needed to turn the gene on in embryonic stem cells," said Professor Jennifer Mitchell of U of T's Department of Cell and Systems Biology, lead invesigator of a study published in the December 15 issue of *Genes & Development*.

"Like the gene itself, this region of the genome enables these stem cells to maintain their ability to become any type of cell, a property known as pluripotency. We named the region of the genome that we discovered the Sox2 control region, or SCR," said Mitchell.

Since the sequencing of the human genome was completed in 2003, researchers have been trying to figure out which parts of the genome made some people more likely to develop certain diseases. They have found that the answers are more often in the regions of the human genome that turn genes on and off.

"If we want to understand how genes are turned on and off, we need to know where the sequences that perform this function are located in the

genome," said Mitchell. "The parts of the human genome linked to complex diseases such as heart disease, cancer and neurological disorders can often be far away from the genes they regulate, so it can be dificult to figure out which gene is being affected and ultimately causing the disease."

It was previously thought that regions much closer to the Sox2 gene were the ones that turned it on in embryonic stem cells. Mitchell and her colleagues eliminated this possibility when they deleted these nearby regions in the genome of mice and found there was no impact on the gene's ability to be turned on in embryonic stem cells.

"We then focused on the region we've since named the SCR as my work had shown that it can contact the Sox2 gene from its location 100,000 base pairs away," said study lead author Harry Zhou, a former graduate student in Mitchell's lab, now a student at U of T's Faculty of Medicine. "To contact the gene, the DNA makes a loop that brings the SCR close to the gene itself only in embryonic stem cells. Once we had a good idea that this region could be acting on the Sox2 gene, we removed the region from the genome and monitored the effect on Sox2."

The researchers discovered that this region is required to both turn Sox2 on, and for the embryonic stem cells to maintain their characteristic appearance and ability to differentiate into all the cell types of the adult organism.

"Just as deletion of the Sox2 gene causes the very early embryo to die, it is likely that an abnormality in the regulatory region would also cause early embryonic death before any of the organs have even formed," said Mitchell. "It is possible that the formation of the loop needed to make contact with the Sox2 gene is an important final step in the process by which researchers practicing regenerative medicine can generate pluripotent cells from adult cells."

"Though the degree to which human embryonic stem cells possess this feature is not entirely clear, by understanding how another complex organism's genome works we ultimately learn more about how our own genome works," said Zhou.

The findings are reported in the article "A Sox2 distal enhancer cluster regulates embryonic stem cell differentiation potential" published online December 15 in *Genes & Development*.

Provided by University of Toronto