Researchers discover a switch that controls stem cell pluripotency

September 15 2011

Scientists have found a control switch that regulates stem cell "pluripotency," the capacity of stem cells to develop into any type of cell in the human body. The discovery reveals that pluripotency is regulated by a single event in a process called alternative splicing.

Alternative splicing allows one gene to generate many different genetic messages and protein products. The researchers found that in genetic messages of a gene called FOXP1, the switch was active in embryonic stem cells but silent in "adult" cells—those that had become the specialized cells that comprise organs and perform functions.

"It opens the field to the fact that alternative splicing plays a really important role in stem cell pluripotency," said Prof. Benjamin Blencowe, principal investigator on the study and a Professor in the University of Toronto's Departments of Molecular Genetics and Banting and Best Department of Medical Research. "We're beginning to see an entirely new landscape of regulation, which will be crucial to our understanding of how to produce more effective pluripotent stem cells for therapeutic and research applications."

The findings were published in the current online edition of the scientific journal *Cell*.

Alternative splicing works by allowing different segments of genetic messages, also known as messenger RNAs, to be spliced in different combinations as the messages are copied from a gene's DNA. Those

combinations make different messenger RNAs, which in turn become different proteins.

In stem cells, scientists have shown that a core set of proteins called transcription factors control pluripotency.

The splicing event discovered by Blencowe's team, including first author on the study Dr. Mathieu Gabut, changes the DNA binding properties of FOXP1 in a way that then controls the expression of the core pluripotency transcription factors, to facilitate maintenance of pluripotency. "As a mechanism that controls those core transcription factors, it's right at the heart of the regulatory process of pluripotency," said Blencowe.

At the same time, the mechanism represses the genes required for differentiation—the process whereby by a stem cell loses "stemness" and becomes a specific cell type that makes up an organ or performs a function.

As well, in collaboration with colleagues including Profs. Jeff Wrana and Andras Nagy in the Samuel Lunenfeld Research Institute at Mount Sinai Hospital, also Professors in U of T's Department of Molecular Genetics, the splicing switch identified by Blencowe's team was shown to play a role in "reprogramming," a potentially therapeutic technique in which researchers coax adult cells back into induced pluripotent stem cells by introducing the core transcription factors. "That's an important area in the field where we need better understanding because reprogramming, especially with human cells, is very inefficient," said Blencowe. "Often when reprogrammed stem cells are not fully reprogrammed they become tumorigenic and can lead to cancer."

Potential applications for stem-cell science include growing cells and tissues to test new drugs or to repair or replace damaged tissues in many

diseases and conditions, including heart disease, diabetes, spinal cord injury and Alzheimer's disease.

As well, a better understanding of the mechanisms that regulate pluripotency, cell division and differentiation will provide knowledge of how diseases like cancer arise and suggest more targeted therapeutic approaches.

Blencowe and his lab have recently turned their attention to what might be controlling the factors that control both alternative splicing and the maintenance of stem-cell pluripotency. They have, said Blencowe, a few tantalizing glimpses. "There's still a lot to figure out, but I personally believe there is huge potential in the future. If we can fully understand the regulatory controls that allow us to make uniform populations of fully reprogrammed stem cells, there's no reason why they shouldn't be effective for many different therapies. It will come."

Provided by University of Toronto