Researchers develop a method for controlling gene activation

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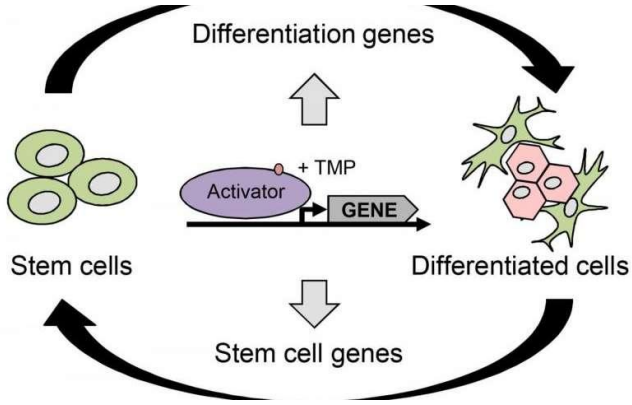

Researchers have developed a method that enables the regulation of a single gene's behavior without changing the genome itself. Credit: Professor Otonkoski Lab, University of Helsinki

Researchers at the University of Helsinki, Finland, have developed a new method which enables the activation of genes in a cell without changing the genome. Applications of the method include directing the differentiation of stem cells.

The method was developed by young researchers Diego Balboa and Jere Weltner, who are working on their doctoral dissertations at Professor Timo Otonkoski's laboratory at the Meilahti medical campus of the University of Helsinki. The research was published in the *Stem Cell Reports* journal, which is a leading publication in the field of stem cell research.

The hottest topics in stem cell research at the moment are methods that can regulate the differentiation of cells. The differentiation process is based on how genes in a cell are activated and deactivated, so researchers are looking for ways to control the activation of the genes. The researchers dream of being able to activate and deactivate genes precisely at specific moments.

"We can produce undifferentiated stem cells from specialised cells, also known as iPS, or induced pluripotent stem cells, and we can regulate the differentiation of these cells by providing them with the right kinds of growth environments. However, we cannot control the differentiation process sufficiently - the process may go smoothly, but then at the very end, a single gene won't activate at the necessary time, and the cell remains immature," Otonkoski explains.

The system of clustered regularly interspaced short palindromic repeats, or CRISPR, means genes can be edited by cutting the DNA at certain points. The method can be used to remove a faulty gene from a cell or to introduce a transplanted gene that will express in the desired way.

Researchers in Otonkoski's laboratory have now developed a method that enables the regulation of a single gene's behaviour without changing the genome itself. The method employs CRISPR technology, but the regulation itself is controlled by the addition of chemicals. The desired gene is made receptive to the drug by introducing bits of RNA into the cell that will bind to the activator protein and the gene's regulatory area. The gene will then activate in the desired way when the chemicals that regulates the activator protein are provided to the cell.

"In our research, we used two common antibiotics, doxycycline and trimethoprim, and these chemicals enabled us to regulate the expression of many genes precisely and effectively. The method worked on all cells we tested, including stem cells - we used human cells in our development," Otonkoski explains.

Professor Otonkoski emphasises that the method is currently being used in experimental models - it is far too early to discuss therapeutic applications.

"The basic idea has now been developed, and the

method has been demonstrated to be viable, and I believe that it can become a very important research tool. In my laboratory we use the method to regulate the differentiation of stem cells, but it has many potential applications in other research fields - for example, in cancer biology."

More information: Diego Balboa, Jere Weltner, Solja Eurola, Ras Trokovic, KirmoWartiovaara, and Timo Otonkoski: Conditionally Stabilized dCas9 Activator for Controlling Gene Expression in Human Cell Reprogramming and Differentiation. *Stem Cell Reports*, September 8, 2015.

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