Reprogrammable cell type depends on a single gene to keep its identity

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Scientists at St. Jude Children's Research Hospital have discovered that a certain differentiated cell type is so ready to change its identity that it requires the constant expression of a gene called Prox1 to dissuade it.

The researchers showed that Prox1 acts as a two-way switch whose inactivity is sufficient to reprogram a specialized type of cell, called a lymphatic endothelial cell (LEC). In the absence of active Prox1, the LEC actually loses its identity and assumes characteristics of a blood endothelial cell (BEC), which plays a different role in the body. Endothelial cells line the inside of blood and lymphatic vessels. The results of the study appear in the Dec. 1, 2008, issue of the journal *Genes & Development*.

The new finding is important because it helps to explain how during embryogenesis a critical set of vessels called the lymphatic vasculature arises from veins; and how lymphatic vessels can eventually lose their characteristics and acquire features typical of blood vessels and transport blood—a trick that might, for example, let the body quickly build up a supply of additional blood vessels when there is an emergency need for more nourishment in a certain area. A switch from lymphatic to blood vessels might also be triggered by certain tumors trying to nourish their own growth.

The lymphatic vasculature is a vital network of vessels that performs important housekeeping functions in the body. Specifically, it drains fluids that normally escape from capillaries, which provide nutrients to

the body's cells. The lymphatic vasculature is also part of the immune system that traps and attacks invading organisms and is a primary route for malignant tumor dissemination to the regional lymph nodes.

"The new finding adds to a growing body of evidence showing that some fully differentiated cell types can exhibit great plasticity and upon reprogramming revert back to their previous identity," said Guillermo Oliver, Ph.D., a member of the St. Jude Department of Genetics and Tumor Cell Biology. Differentiation is the process by which genetic activity causes an immature cell type to acquire specific characteristics of a particular mature adult cell type.

"In the last few years, some discoveries have challenged the long-standing belief that cell differentiation is an irreversible final process," said Oliver, the paper's senior author. "St. Jude researchers showed that lymphatic endothelial cells are one of the few examples of differentiated cell types that require constant expression of a specific gene to maintain their identity. This current work builds on our previous results that demonstrated the key role Prox1 plays in the formation of the lymphatic vasculature."

As an important resource for this finding, Oliver's team used a special mouse strain in which the Prox1 genes could be deleted from LECs at different times during development or after birth.

The St. Jude team found that deletion of Prox1 in LECs promoted their reprogramming into BECs as indicated by the expression of specific LEC and BEC proteins. In addition, the newly reprogrammed cells gained some specific features typical of blood vessels. For example, the cells were surrounded by pericytes—small cells that help support endothelial cells—and blood abnormally entered the reprogrammed mutant lymphatic vessels.

Finally, the researchers used a trick that enabled them to block the ability of isolated cultured LECs to produce the Prox1 proteins to further demonstrate that Prox1 activity is required by LECs to maintain their identity.

"The new insights offered by this research will give us a better understanding of how to convert one cell into another and the eventual use of the new therapeutic approaches in pathological conditions and tumors," Oliver said.

Source: St. Jude Children's Research Hospital

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