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Stem-cell activators switch function, repress mature cells

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In a developing animal, stem cells proliferate and differentiate to form the organs needed for life. A new study shows how a crucial step in this process happens and how a reversal of that step contributes to cancer.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, shows for the first time that three proteins, called E2f1, E2f2 and E2f3, play a key role in the transition stem cells make to their final, differentiated, state.

These proteins help stimulate stem cells to grow and proliferate. But once stem cells begin to differentiate into their final cell type - a cell in the retina or in the lining of the intestine, for example - the same three proteins switch function and stop them from dividing any more.

The research also shows how these proteins can switch course yet again in cells that have mutations in the retinoblastoma (Rb) gene. Mutated Rb genes occur in many types of cancer, suggesting that these E2f proteins might offer a safe and novel therapeutic target in these tumors.

The findings are published in back-to-back papers in the Dec. 17 issue of the journal *Nature*.

"We show that these E2fs are gene activators in stem cells but then switch to gene repressors when stem cells begin differentiating," says Gustavo Leone, associate professor of molecular virology, immunology

and medical genetics at Ohio State's James Cancer Hospital and Solove Research Institute. Leone headed the first of the two *Nature* studies and is a co-author on the second.

"This is a very important step in the process of differentiation," Leone says. "As organs form during development, there comes a time when their growth must stop because an organ needs only a certain number of cells and no more. The switch by these proteins from activators to repressors is essential for that to happen.
"Before this, there was no suspicion that these regulatory proteins had any role in differentiated cells," says Leone. "It was thought they were important only in proliferating cells like stem cells. But that's not true."

Leone and his colleagues show the function of the proteins in differentiation in mouse embryos, retinas, lenses and intestines.

They also show how the three proteins could revert back to gene activators in cancer cells and promote tumor growth in cancers with Rb mutations. "In this case, these proteins are acting abnormally relative to the surrounding tissue, so they might provide a safe therapeutic target," Leone explains. "If we can inactivate these E2fs in cancer cells, perhaps we can prevent further tumor growth without having a major affect on healthy cells."

Provided by Ohio State University Medical Center