Protein kinase Akt identified as arbiter of cancer stem cell fate, paper reports

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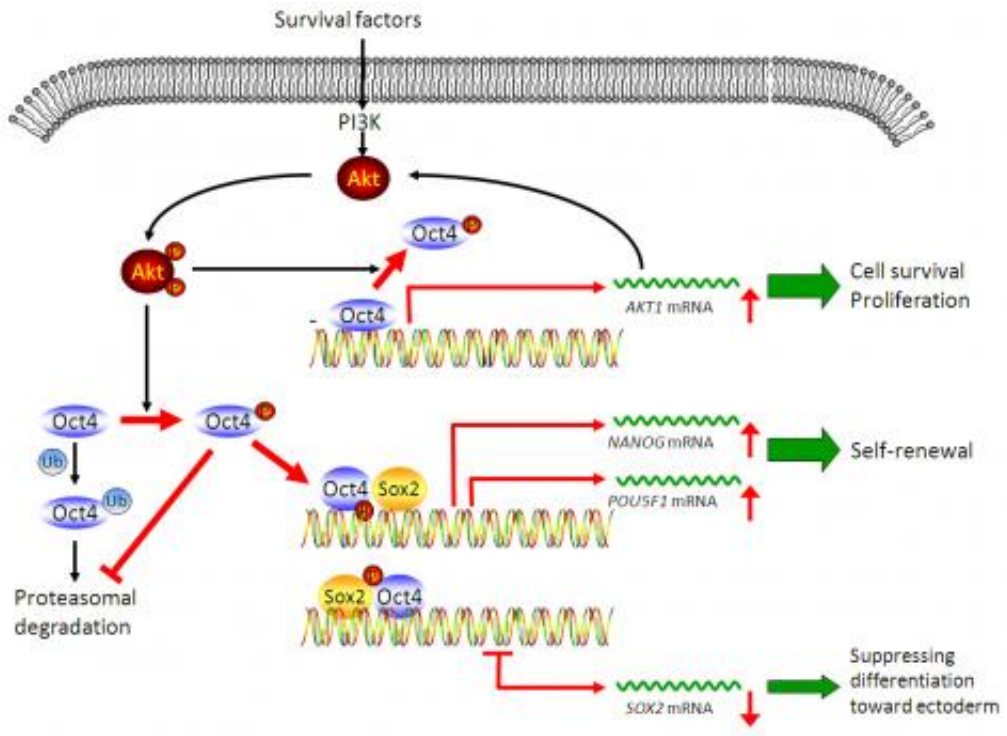

Signaling via the Akt serine/threonine protein kinase plays critical roles in the self-renewal of embryonic stem cells and their malignant counterpart, embryonal carcinoma cells. Credit: Honglin Zhou, Perelman School of Medicine, University of Pennsylvania; Molecular Cell

(Medical Xpress)—The protein kinase Akt is a key regulator of cell growth, proliferation, metabolism, survival, and death. New work on

Akt's role in cancer stem cell biology from the lab of senior author Honglin Zhou, MD, PhD and Weihua Li, co-first author, both from the Center for Resuscitation Sciences, Department of Emergency Medicine, Perelman School of Medicine, University of Pennsylvania, and Xiaowei Xu, Department of Pathology and Laboratory Medicine, appears in *Molecular Cell*. The findings were also highlighted in *Nature* and *Science* reviews.

This new research shows that Akt may be the key as to why cancer stem cells are so hard for the body to get rid of. It has been documented that frequent hyperactivation of Akt kinases occurs in many types of human solid tumors and blood malignancies. Prior to this work, Akt was also shown to play a pivotal role in the fate of other types of stem cells, though those cellular mechanisms are still unclear.

"When I came to Penn in 2009, my lab first found that Akt regulates the activity of the protein Oct4," explains Zhou. Oct4 is one of the four transcriptional factors used to generate induced pluripotent stem cells, or iPS cells. In 2006, Kyoto University researcher and Nobel Prize winner Shinya Yamanaka expressed four proteins – Oct 4 was one of the - in mouse somatic cells to rewind their genetic clocks, converting them into embryonic-like iPS cells.

The biochemical experiments outlined in the *Molecular Cell* paper confirmed that Oct4 interacts directly with Akt and the adding of phosphate molecules to Oct4 by Akt regulates its stability, where it localizes in a cell, and its effect on gene expression. Akt phosphorylating Oct4 has the effect of making Oct4 migrate into the nucleus, where it interacts with other transcription factors and regulates target genes transcription.

The findings were further extended into embryonal carcinoma cells, which are derived from teratocarcinomas and often considered the

malignant counterparts to embryonic stem cells (ESCs). The team showed that embryonal carcinoma cells with deregulated Akt activation and more phosphorylated Oct4 are more resistant to cell death signals such as ultraviolet irradiation and high glucose treatment.

Since Akt activation is often deregulated in cancer and Oct4 expression is upregulated in cancer stem cells of various types of cancer, the researchers are studying whether the Akt/Oct4 pathway plays similar roles in other types of cancer stem cells in addition to embryonal carcinoma cells. If true, Akt inhibitor may be developed as a new drug for killing cancer stem cells in cancer therapy.

More information: Paper: download.cell.com/molecular-ce … 1097276512007745.pdf
stke.sciencemag.org/cgi/conten … ec310?printview=true
www.nature.com/nchina/2012/121 … /nchina.2012.74.html

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