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Researchers identify key players in cancer cells' survival kit

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Dana-Farber Cancer Institute scientists have discovered new details of how cancer cells escape from tumor suppression mechanisms that normally prevent these damaged cells from multiplying. They also demonstrated a potential link between this cell proliferation control mechanism and the cognitive deficits caused by Down syndrome.

The findings add to a still-sparse understanding of how normal and cancerous cell growth is regulated and have potential implications for improved treatments, say the authors of a pair of articles in *Genes & Development*.

James A. DeCaprio, MD, of Dana-Farber said the results may provide new targets both for blocking the progress of cancer and perhaps for facilitating the growth of neurons in the developing brains of infants with Down syndrome.

DeCaprio is the senior author and Larisa Litovchick, PhD, also of Dana-Farber, is the first author of one of the papers. They also are co-authors on the second article, whose senior author is Nicholas Dyson, PhD, at Massachusetts General Hospital Cancer Center. In that report, the researchers revealed a previously unrecognized link between two cell-signaling pathways, called Rb and Hippo in scientific shorthand, that help regulate the formation of cells and organs during early development. Both pathways are frequently disrupted in cancer.

The life of a cell is defined by phases in which it grows, creates a

duplicate set of chromosomes, and divides into two daughter cells -- all governed by external signals such as growth-stimulating factors and internal "checkpoints." Cells can also exit the growth cycle in two ways -- becoming quiescent or inactive (which most of our cells are most of the time) until they re-enter the growth cycle, or senescent. Cells entering senescence are damaged or nearing the end of their lives, and ultimately die.

Cancer cells survive, in part, by ignoring signals to become senescent and continuing to make copies of themselves at will, or by entering a quiescent state from which they can be re-activated. Scientists don't have a good understanding of how cells negotiate the molecular checkpoints that control these transitions.

"Our study identifies a molecular switch required for entry into quiescence and senescence," said DeCaprio, whose laboratory group focuses on cell cycle regulation.

The gatekeeper to cell senescence and quiescence is a group of eight proteins that assemble themselves into the so-called DREAM complex, which helps cells exit the active cycle by turning off more than 800 growth-related genes.

A key player that triggers the assembly of the DREAM team is p130, a member of the Rb family of proteins. DeCaprio said the new research highlights p130's underappreciated role in DREAM action. "We have for the first time linked p130 itself to quiescence and senescence" -- the latter contributing to cancer formation, said DeCaprio, who is also an associate professor of medicine at Harvard Medical School.

The report also for the first time reveals that a molecular switch, an enzyme called DYRK1A, performs a crucial step in assembling the p130-DREAM complex, and thus is novel control point for quiescence

and senescence. When DYRK1A is turned on, it acts through p130 to set in motion the assembly of DREAM, which turns off the growth genes and allows cells to depart the growth cycle and become quiescent or senescent.

DYRK1A's ability to turn off cell growth genes may also be involved in the lower-than-normal development of brain neurons in Down syndrome, say the scientists, who are investigating possible new avenues to treating the disorder.

While they tend to have cognitive losses, people with Down syndrome have a markedly lower risk of most types of cancer. DYRK1A is made by a gene on chromosome 21, which is present in three copies instead of the normal two in people with Down syndrome, causing the enzyme to be overproduced. DeCaprio said this abnormal activity could explain both outcomes: DYRKIA-triggered DREAM formation could help suppress cancers by driving them into senescence, and also reduce the generation of brain cells during development.

The second paper in Genes & Development describes a functional connection between the Hippo signaling pathway and the Rb pathway that contains DYRK1A. The researchers showed that a component of the Hippo pathway, a protein called LATS2, can activate DYRK1A.

The authors said that LATS2 gene is located in an area frequently missing in cancer cells, suggesting that LATS2 might be a new control point for suppressing cancer cell growth.

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