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Scientists uncover inflammatory circuit that triggers breast cancer

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Although it's widely accepted that inflammation is a critical underlying factor in a range of diseases, including the progression of cancer, little is known about its role when normal cells become tumor cells. Now, scientists from the Florida campus of The Scripps Research Institute have shed new light on exactly how the activation of a pair of inflammatory signaling pathways leads to the transformation of normal breast cells to cancer cells.

The study, led by Jun-Li Luo, an assistant professor at Scripps Florida, was published online before print by the journal *Molecular Cell* on February 23, 2012.

The scientists' discovery points to the activation of a self-sustaining signaling circuit that inhibits a specific RNA, a well-known tumor suppressor that helps limit the spread of cancer (metastasis). Therapies that disable this circuit and halt this miRNA repression could have the potential to treat cancer.

The Spark that Ignites Trouble

In the new study, scientists identified the specific pathways that transform breast epithelial cells into active cancer cells.

The researchers found immune/inflammatory cells ignite the transient activation of MEK/ERK and IKK/NF-kB pathways; the MEK/ERK

pathway then directs a consistent activation of a signaling circuit in transformed cells. This consistent signaling circuit maintains the malignant state of the tumor cells.

Luo compares this process to starting a car—a car battery starts the engine much like the transient signal activation turns on the consistent signal circuit. Once the engine is started, it no longer needs the battery.

The scientists go on to show that the initial activation of these pathways also activates IL6, a cytokine involved in a number of inflammatory and autoimmune diseases, including cancer. IL6 acts as a tumor initiator, sparking the self-sustaining circuit in normal breast cells necessary for the initiation and maintenance of their transformed malignant state.

In establishing that self-sustaining signal circuit, IL6 represses the action of microRNA-200c, which is responsible for holding down inflammation and cell transformation. Since enhanced microRNA-200c expression impairs the growth of existing cancer cells and increases their sensitivity to anti-tumor drugs, compounds that disable microRNA-200c repression have the potential to act as a broad-spectrum therapeutic.

Interestingly, the new findings dovetail with the "multiple-hits theory" of tumor formation, which posits that once normal cells in the human body accumulate enough pre-cancerous mutations, they are at high-risk for transformation into tumor cells. While the newly described initial pathway activation is momentary and not enough to cause any lasting changes in cell behavior, it may be just enough to tip the cell's transformation to cancer, especially if it comes on top of an accumulation of other cellular changes.

More information: The first author of the study, "IL6-Mediated Suppression of Mir-200c Directs Constitutive Activation of an Inflammatory Signaling Circuit That Drives Transformation and

Tumorigenesis," is Matjaz Rokavec of Scripps Research. Other authors include Weilin Wu, also of Scripps Research.

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