Crosstalk between critical cell-signaling pathways holds clues to tumor invasion and metastasis

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Two signaling pathways essential to normal human development - the Wnt/Wingless (Wnt) and epidermal growth factor receptor (EGFR) pathways - interact in ways that can promote tumor cell invasion and metastasis, researchers from The University of Texas M. D. Anderson Cancer Center report in the Nov. 25 issue of *Molecular Cell*.

This newly characterized interaction involves three signaling components known to correlate with invasive cancer - activation of EGFR, elevated protein kinase CK2 activity, and increased beta-catenin - T-cell factor/lymphoid enhancer factor (TCF/LEF-1) transcriptional activity.

"These findings highlight the importance of Wnt-independent and non-canonical activation of beta-catenin in tumor development," said senior author Zhimin Lu, MD, PhD, an associate professor in M. D. Anderson's Department of Neuro-Oncology. They also open up new possibilities for biomarkers that indicate prognosis or guide treatment.

Wnt Signaling and Cell-to-Cell Adhesion

Cell signaling is an intricate and precise process that enables cells to grow, differentiate (become specialized) and ultimately die (apoptosis). This orderly process is responsible for the normal development of organs and tissues. Alterations in the signaling within cells and between cells, however, can disrupt the cell-to-cell contact that helps keeps tumor cells in place. Loss of cell-to-cell contact leads to tumor cell migration, invasion and metastasis.

The Wnt signaling pathway plays a critical role in cell development, proliferation and differentiation. Mutations in this important pathway leading to the activation of beta-catenin are responsible for many types of cancer, including colon cancer. However, beta-catenin can also be activated in a mutation-independent manner in other cancers.

A key component of the Wnt pathway, beta-catenin combines with alpha-catenin and regulates cell-cell adhesion. It also interacts with alpha-catenin in the nucleus.

The alpha-catenin component of this beta-catenin/alpha-catenin complex has an inhibitory effect on beta-catenin that helps keep tumor cell migration and invasion in check. This inhibition is lost, however, when the EGFR pathway is activated. Upon activation, beta-catenin becomes untethered from alpha-catenin and translocates to the cell nucleus, where it increases expression of key target genes involved in tumor cell invasion and metastasis.

New Pathway Regulates Beta-Catenin Transactivation

The M. D. Anderson-led team made a surprising discovery: Beta-catenin also can travel to the nucleus via activation of the EGFR pathway-and it does so independently of Wnt signaling or mutations. The newly described pathway disrupts the beta-catenin/alpha catenin complex through an EGFR-extracellular receptor kinase (ERK)-protein kinase CK2- phosphorylation cascade. The investigators noted that this cascade culminates in the phosphorylation of alpha-catenin and ultimately promotes beta-catenin activation in the nucleus and subsequent tumor cell invasion.

The researchers found evidence of the newly identified pathway's clinical relevance when they examined human glioblastoma specimens. Specifically, levels of alpha-catenin phosphorylation correlated with levels of ERK activity and with grades of malignancy.

"Taken together, these findings demonstrate the importance of this pathway in tumor formation and progression," Dr. Lu said, "and they reveal potential markers for prognosis and therapeutics." Dr. Lu's lab is currently identifying genes downstream from beta-catenin that may be instrumental in tumor progression.

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