MedicalXpress

Study indicates possible new way to treat endometrial, colon cancers

October 2 2014

Scientists love acronyms. In the quest to solve cancer's mysteries, they come in handy when describing tongue-twisting processes and pathways that somehow allow tumors to form and thrive. Two examples are ERK (extracellular-signal-related kinase) and JNK (c-June N-Terminal Kinase), enzymes that may offer unexpected solutions for treating some endometrial and colon cancers.

A study led by Gordon Mills, M.D., Ph.D., professor and chair of Systems Biology at The University of Texas MD Anderson Cancer Center with Lydia Cheung, Ph.D. as the first author, points to cellular mutations in the gene PIK3R1 which activate ERK and JNK, thus allowing tumor growth. Results from the study, were published in this month's issue of *Cancer Cell*.

The PIK3R1 gene has been thought to impact the PI3K pathway since its discovery over two decades ago. The PI3K signaling pathway has long been known to play a role in cancer cell proliferation, and targeting why and how PI3K allows tumor cells to grow has been an important area of study and treatment.

"We found that the PIK3R1 mutation, R348, is a "neomorph" that changes the very nature of the gene itself, and unexpectedly activates the ERK and JNK signaling cascades rather than the normal PI3K pathway. Mutations in close proximity to R348 exhibit the same effects," said Cheung.

Standard therapies today center on the cancer gene as a whole. Mills' and Cheung's study suggests that targeted therapies may need to focus on the gene mutation specifically.

"Our findings uncovered an unexpected neomorphic role for a subset of PIK3R1 mutations that may provide a rationale for therapeutic targeting of these mutant tumors. Indeed, we are very encouraged by preclinical findings," said Mills. "PIK3R1 mutations are particularly prevalent in endometrial and colon cancers."

According to data from The Cancer Genome Atlas (TCGA), PIK3R1 mutations are one of the most common gene aberrations seen in over 4,400 tumor types and 20 cancers and appears to be the twelfth most commonly mutated gene in cancer The Cancer Genome Atlas is a research program supported by the National Cancer Institute and National Human Genome Research Institute within the National Institutes of Health that is looking at genomic changes in more than 20 different types of cancer.

Tumors form because cells refuse to die when they are genetically programmed to do so. The PIK3R1 neomorphic mutations prevent cell death by activating ERK and JNK. If a therapy can be developed that would stop this chemical collusion, then there may be the potential for halting tumor growth. Such therapies are being evaluated for other aberrations across many cancer types including an endometrial cancer study at MD Anderson.

"The effective implementation of targeted therapy ultimately lies in the individualization of treatment regimens based on targeting specific mutations," said Mills. "Our studies show that the cancer gene aberration rather than the cancer gene alone will need to be considered for effective therapy."

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Provided by University of Texas M. D. Anderson Cancer Center

Citation: Study indicates possible new way to treat endometrial, colon cancers (2014, October 2) retrieved 2 May 2024 from https://medicalxpress.com/news/2014-10-endometrial-colon-cancers.html

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