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Mechanism of lung cancer-associated mutations suggests new therapeutic approaches

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Vanderbilt-Ingram Cancer Center researchers have identified how one of the genes most commonly mutated in lung cancer may promote such tumors.

The investigators found that the protein encoded by this gene, called EPHA3, normally inhibits tumor formation, and that loss or mutation of the gene – as often happens in lung cancer – diminishes this tumor -suppressive effect, potentially sparking the formation of lung cancer. The findings, published July 24 in the *Journal of the National Cancer Institute,* could offer direction for personalizing cancer treatments and development of new therapies.

The ephrin family of receptors (EPH receptors) comprises a large group of cell surface proteins that regulate cell-to-cell communication in normal development and disease. EPH receptor mutations have been linked to several different cancer types.

Jin Chen, M.D., Ph.D., professor of Medicine, Cancer Biology and Cell & Developmental Biology, studies the cancer-associated roles of these receptors. While her lab has focused primarily on EPHA2 (and its role in promoting breast cancer and tumor blood vessel formation), she decided to look at a different ephrin receptor based on the findings of large genomic screens of lung tumors.

"A 2008 genome-wide study published in Nature identified 26 genes as potential drivers of lung cancer," Chen said. "One of them was EPHA3."

That study and others suggested that mutations in EPHA3 were present in 5 percent to 10 percent of lung adenocarcinomas. However, the studies did not reveal how these mutations might promote tumor formation or progression.

Chen wanted to investigate further whether mutations in EPHA3 were actually "drivers" of lung cancer or just neutral "passenger" mutations and how the mutations might promote tumor growth.

The researchers generated and analyzed 15 different mutations in the receptor. They found that at least two functioned as "dominant negative" inhibitors of the EPHA3 protein – that is, having a mutation in just one allele (or "copy" – humans have two copies of each gene) was enough to inhibit the function of EPHA3.

Chen and colleagues determined that normal or "wild type" EPHA3 inhibits a downstream signaling pathway (the Akt pathway) that promotes cell survival – so, normally, activation of EPHA3 acts as a "brake" on cell growth and survival and induces programmed cell death (apoptosis). When one EPHA3 allele is lost (due to a mutation), the receptor cannot be activated and the Akt pathway remains active, which promotes cell growth and survival.

To determine the impact of EPHA3 mutations on human lung cancer cases, biostatisticians Yu Shyr, Ph.D., and Fei Ye, Ph.D., helped Chen's group identify a mutational signature from existing patient data that strongly correlated with poor patient survival. The team also found that both gene and protein levels of EPHA3 were decreased in patient lung tumors.

While previous studies had linked EPHA3 mutations to lung cancer, the current study is the first to "connect the dots."

"The EPH family is such a big family that nobody had really connected the data from bench top – from the cell and biochemical studies – to human data," Chen said.

Together, the findings suggest that mutations in EPHA3 may be important drivers of a significant fraction of lung cancers. And the research team's identification of the biochemical and cellular consequences of EPHA3 mutations suggests that therapies that target a downstream pathway (such as Akt) might be beneficial for tumors with mutant EPHA3.

Provided by Vanderbilt University Medical Center