Oncogene inhibits tumor suppressor to promote cancer: Study links B-RAF and LKB1

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Scientists have uncovered an interesting connection between two important protein kinase signaling pathways that are associated with cancer. The research, published by Cell Press in the January 30th issue of the journal *Molecular Cell*, may direct new therapeutic strategies for multiple types of cancer.

The protein kinase LKB1 is a known tumor suppressor and the LKB1-AMPK signaling pathway couples energy metabolism with cell growth, proliferation and survival. "Mutations in LKB1 are not frequent in human cancers and it is not clear how tumor cells suppress the signaling pathway to gain growth advantage under conditions of energy stress (common in cancer cells)," explains senior study author Dr. Lewis C. Cantley from Beth Israel Deaconess Medical Center and Harvard Medical School.

Dr. Cantley and colleagues, including Dr. Bin Zheng, designed a study to investigate the molecular mechanisms associated with suppression of the LKB1-AMPK pathway in tumor cells. The researchers used malignant melanoma cells that often have a mutation called "V600E" in the RAF protein B-RAF. The RAF-MEK-ERK pathway is well established as a key regulator of cell growth, proliferation, differentiation and survival.

Mutations in the RAF kinase B-RAF have been found in many types of human cancer but, while oncogenic B-RAF V600E has been linked with tumor induction, growth, maintenance and progression, the specific molecular mechanisms have not been identified. Dr. Cantley's group found that melanoma cells with the B-RAF V600E mutation had impaired AMPK activation and that inhibition of B-RAF signaling activated AMPK.

The researchers went on to show that LKB1 was phosphorylated by two kinases that are downstream of B-RAF, ERK and Rsk. The phosphorylation of LKB1 interfered with the ability of LKB1 to bind and activate AMPK. Importantly, expression of mutant LKB1 that could not be phosphorylated resulted in activation of AMPK and an inhibition of melanoma cell proliferation.

"Taken together, our results provide a molecular linkage between the LKLB1-AMPK and the RAF-MEK-ERK pathways and suggest that suppression of LKB1 function by B-RAF V600E plays an important role in B-RAF V600E-driven tumorigenesis," says Dr. Zheng. "It's conceivable that tumor cells must turn off the LKB1-AMPK signaling pathway to gain a growth advantage under conditions of energy stress."

Given that B-RAF mutation and loss of LKB1 are associated with multiple types of cancer, the work is likely to have a significant clinical impact. "Further understanding of how the intriguing molecular linkage between LKB1-AMPK and RAF-MEK-ERK functions in tumorigenesis could potentially provide great therapeutic opportunities for cancer treatment," offers Dr. Cantley.

Source: Cell Press