Selective inhibition of BMK1 suppresses tumor growth

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A study describing a newly developed pharmacological inhibitor is providing detailed insight into how an enzyme that has been implicated in multiple human malignancies regulates a known tumor suppressor. The research, published by Cell Press in the September 14th issue of the journal *Cancer Cell*, may have broad application for treating human cancers.

Mitogen-activated protein kinases (MAPKs) are enzymes that regulate multiple cellular activities, including proliferation and cell survival. Mutations in MAPK signaling pathways have been shown to play a significant role in many types of cancer. Of the four different MAPKs that have been identified in mammalian cells, ERK1/2 and BMK1 exhibit significant structural similarity. In fact, recent research has shown that some pharmacological compounds which have been considered to be specific inhibitors of ERK1/2, also interfere with the lesser known BMK1.

"It is critical that results using the common MAPK inhibitors be reevaluated using more specific inhibitors of the BMK1 and ERK1/2 cascades. However, so far there has been no specific small-molecule inhibitor of BMK1 that is effective both in cells and animals," explains senior study author, Dr. Jiing-Dwan Lee, from The Scripps Research Institute in La Jolla, California. "More importantly, the lack of this kind of BMK1 inhibitor has hampered the understanding of the physiological/pathological roles of BMK1."

Dr. Lee and colleagues discovered that promyelocytic leukemia protein (PML), which is a known tumor suppressor, is inhibited by BMK1. "Previous reports had implicated ERK1/2 in the regulation of PML," says Dr. Lee. "However, in our study we found that that BMK1 interacts with PML and suppresses its antitumor actions." To further investigate the BMK1-PML interaction, the researchers developed a compound called XMD8-92 that was remarkably selective at inhibiting BMK1.

Treatment with XMD8-92 blocked tumor cell proliferation and significantly inhibited tumor growth in mice. Importantly XMD8-92 had no obvious negative effects on the animals. "These results demonstrate that the BMK1 pathway can be blocked effectively by a small-molecule inhibitor without apparent adverse effects and, more importantly, BMK1 inhibition is a very effective way to prevent cancer development in animals," concludes Dr. Lee. "As BMK1 is expressed in most tumor cells, our results suggest that cancer therapies targeting BMK1 may be useful for treating diverse types of human tumors."

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