

Cancer therapy: A role for MAPK inhibitors combined with mTORC1 inhibitors

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Nearly a decade ago, while it was being tested as an immunosuppressive agent to prevent organ rejection in transplant patients, the drug rapamycin was also discovered to have anti-tumor properties. Since then, several rapamycin analogs known as mTOR (mammalian target of rapamycin) inhibitors have been tested in clinical trials for the treatment of various types of cancer.

But despite promising early results, mTOR inhibitors have proven less successful than originally expected.

Now research led by scientists at Beth Israel Deaconess Medical Center (BIDMC) identifies a previously unrecognized problem faced by these agents when it comes to attacking cancers. Reported in the August 21 advance on-line issue of *The Journal of Clinical Investigation (JCI)*, the new findings show that at the same time that rapamycin analogs are halting tumor growth by inhibiting the mTOR protein complex 1 (mTORC1), they are activating the MAPK (mitogen-activated protein kinase) pathway -- thereby encouraging cancer cell survival.

"Anticancer research is aimed at understanding the molecular pathways that can be selectively targeted to halt tumor growth," explains senior author Pier Paolo Pandolfi, MD, PhD, Director of Basic Research of the Cancer Center at BIDMC and Professor of Medicine at Harvard Medical School. "We know that the mTOR pathway is activated in many cancers, and therefore, is a good target for fighting a wide array of tumors."

The mTOR pathway controls cell growth and angiogenesis through a series of mechanisms that integrate signaling from nutrients and other growth-promoting pathways. Activation of mTOR, therefore, promotes the proliferation of tumor cells, while inhibition of mTOR counters this action. However, because the mTOR signaling pathway is extremely complex, scientists have focused their efforts on identifying other agents that could be successfully combined with mTOR inhibitors to halt cancer growth.

The new findings shine a light on MAPK, a signaling pathway also known for its role in sensing growth factors to promote cell survival and proliferation.

"We analyzed tissue from human biopsies, as well as cancer cell lines and genetically engineered mouse models of cancer," explains the study's first author Arkaitz Carracedo, PhD, a postdoctoral fellow in the Pandolfi laboratory. "These experiments all pointed to the MAPK pathway."

From there, Carracedo and his coauthors went on to test a group of MAPK inhibitor agents to find out if, in combination with mTOR inhibitors, the agents would act to counter any pro-survival activity. And they did.

"This study inserts a new piece of information into the puzzle of the effects of mTORC1 inhibitors in cell signaling," says Pandolfi.

"Furthermore, because there are inhibitors of MAPK pathway already approved for the treatment of cancer, it provides us with the rationale for using combinations of mTORC1 and MAPK inhibitors in attacking tumors, thereby offering cancer patients another treatment option with immediate applicability."

Source: Beth Israel Deaconess Medical Center

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