# Treatment with PI3K inhibitors may cause cancers to become more aggressive and metastatic

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Dario C. Altieri, M.D., is the president and CEO of The Wistar Institute, director of The Wistar Institute Cancer Center, and the Robert and Penny Fox Distinguished Professor. Credit: The Wistar Institute

The enzyme phosphatidylinositol-3 kinase (PI3K) appears to be exploited in almost every type of human cancer, making it the focus of considerable interest as a therapeutic target, with many PI3K-inhibiting drugs currently in various stages of clinical development. However, PI3K inhibitors have only shown modest clinical activity with patients who receive these drugs experiencing very little improvement in survival.

Now, new research from scientists at The Wistar Institute shows that treatment with PI3K inhibitors alone may actually make a patient's cancer even worse by promoting more aggressive tumor cell behavior and increasing the cancer's potential of spreading to other organs.

The findings were published online by the journal *Proceedings of the National Academy of Sciences*.

Many cancer researchers consider PI3K to be a "master switch" that enables cell proliferation, cell survival and metastasis, the dissemination of tumor cells throughout the body. Despite PI3K's appeal as a target, patients who receive PI3K inhibitors soon become resistant to the drugs after treatment.

Drug resistance is considered one of the most important barriers to achieving long-lasting remissions or even cures, and considerable effort is being devoted to garner a better understanding of how tumors adapt to therapy, allowing them to maintain their continued growth and metastatic potential.

In this study, a team of researchers led by Dario C. Altieri, M.D., President and CEO of The Wistar Institute, director of Wistar's Cancer Center and the Robert and Penny Fox Distinguished Professor, focused on the role of the mitochondria - the "powerhouse" of the cell responsible for energy production - in tumors. Specifically, they looked

at how these mitochondria are reprogrammed when exposed to PI3K inhibition and how these energy sources might prevent targeted agents from being as effective as expected.

"Our prior studies have confirmed that tumor cells rely on energy produced by mitochondria more significantly than previously thought," Altieri said. "What we have shown in this study is that, in somewhat of a paradox, treatment with a PI3K inhibitor causes a tumor cell's mitochondria to produce energy in a localized manner, promoting a far more aggressive and invasive phenotype. The treatment appears to be doing the opposite of its intended effect."

The study showed that treatment with a PI3K inhibitor causes the mitochondria to migrate to the peripheral cytoskeleton of the tumor cells. While the mitochondria in untreated cells cluster around the cell's nucleus, exposure of tumor cells to PI3K therapy causes the mitochondria to move to specialized regions of the cell's membrane implicated in cell motility - meaning that the cell is able to move spontaneously - and invasion. In this "strategic" position, tumor mitochondria are ideally positioned to provide a concentrated source of energy to support an increase in cell migration and invasion.

While PI3K-targeted therapies appear to paradoxically promote a more aggressive tumor behavior, the dependence of this response on mitochondrial function may offer a new therapeutic angle. Altieri and his team have shown that targeting mitochondrial functions for tumor therapy is feasible and dramatically enhances the anticancer activity of PI3K inhibitors when used in combination.

"These findings continue to support the idea that the mitochondria of tumor cells are crucial to tumor survival and proliferation," Altieri said. "It's certainly counterintuitive that a drug designed to fight cancer may in actuality help it spread, but by identifying why this is happening, we can

develop better strategies that allow these drugs to treat tumors the way they should."

**More information:** PI3K therapy reprograms mitochondrial trafficking to fuel tumor cell invasion, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1500722112

Provided by The Wistar Institute