Novel combination therapy may help overcome mTOR drug resistance in AML

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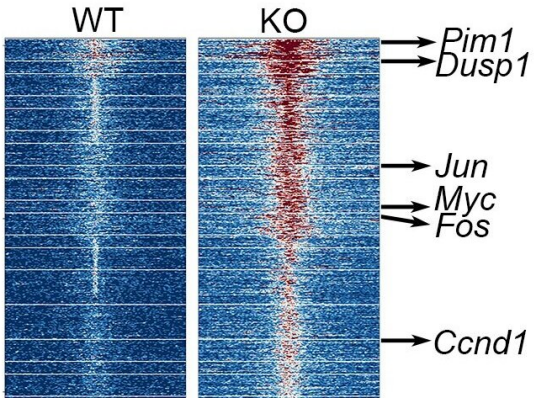

This genetic "heat map" shows that several key genes associated with cell proliferation become more active in mice bred to lack the mTOR gene. This activity helps build signaling pathways that can allow cancerous cells to avoid disruption from mTOR inhibitors, according to a study in PNAS led by experts at Cincinnati Children's. Credit: Cincinnati Children's

Soon after rapamycin, the first mTOR inhibitor, emerged in 1990s as a potential treatment against unwanted cell proliferation, many cancer experts had hoped emerging drugs targeting mTOR would become a breakthrough targeted therapy for children and adults suffering relapses of acute myeloid leukemia (AML) and other cancers where mTOR activity is abnormally high.

However, numerous clinical trials involving three generations of mTOR inhibitors have found that cancer cells possess a remarkable ability to make new cells that dodge these drugs. The repeated disappointments partially explain why some people with AML treated with mTOR inhibitors develop fatal relapses despite so many improvements in leukemia outcomes over the years.

"Overcoming resistance to therapy remains a holy grail of leukemia treatment," says Yi Zheng, Ph.D., Director, Experimental Hematology and Cancer Biology at Cincinnati Children's. "While mTOR is a recognized target for AML and many cancers, inhibitor trials have not gone as expected."

Now, research led by Zheng and colleagues at Cincinnati Children's suggests a novel method for boosting the effectiveness of mTOR inhibitors. While the latest study is based on mouse models, building upon the findings published Dec. 21, 2020, in *PNAS* eventually could improve outcomes for people with AML, and possibly other forms of cancer.

How mTOR inhibitors trigger an alarm

Many scientists have documented the multipurpose role played by the mechanistic target of rapamycin (mTOR) protein. The protein is involved in regulating cell growth, survival, metabolism, and immunity. Disruptions to normal mTOR activity have been implicated in several types of cancer and other conditions. Thus targeting the mTOR signaling pathway has become a frequently traveled line of research.

The new research from Cincinnati Children's sheds new light on what happens when treatments target mTOR.

"Using a novel mouse model, we have learned that deleting the mTOR gene prompts blood stem cells to multiply rapidly to open other pathways to continue producing new blood cells. We also found that leukemia cells use a similar response to continue multiplying despite mTOR-inhibiting treatments," says the study's senior author Yi Zheng, Ph.D.

Attacking mTOR essentially sets off alarms among hemopoietic stem cells (HSCs), which act like blood cell factories deep in bone marrow. In response, the HSCs themselves begin hyperproliferation, which produces a flood of new, re-wired blood cells.

Similarly, re-wired cancer stem cells treated with mTOR inhibitors can also begin multiplying using new signaling pathways instead of mTOR. Soon, the new cancer cells render mTOR inhibitor drugs useless.

Defeating the security system

Somewhat like would-be robbers hacking the bank's alarm code, Zheng's team figured out how blood stem cells in mice rewire themselves when mTOR gene activity is deleted.

Using a combination of genetic analysis tools including RNA-seq, ChIP-seq, and ATAC-seq, the team determined that HSCs respond to loss of mTOR by activating the ERK/MNK/eIF4E signaling pathway. This enhances the protein translation of RNA polymerase II, which in turn boosts c-Myc gene expression—and that allows both normal HSCs and leukemic stem cells to thrive.

The good news? Some drugs already are known to work against this alternate signaling pathway, which suggests that a combination therapy could use an mTOR inhibitor to directly attack AML cell production while using other drugs to cut off alternative production paths.

The co-authors say mTOR treatment resistance can be counteracted by inhibiting activity of the MNK gene, CDK9 or c-Myc. So-called BET inhibitors can act against c-Myc activity. Other inhibitors that are in clinical trials can act against CDK9.

Next steps

Scientists at Cincinnati Children's have already launched some of the research needed to prepare the combination therapies for in vivo test leading to human clinical trials, Zheng says. That process will take time, but since mTOR inhibitors have been widely tested in clinical trials, investigators have a head start on exploring combination therapies.

Longer term, the findings may extend beyond AML, Zheng says, because mTOR has been a recognized target in most human cancers, including solid tumors like brain tumors.

More information: Cuiqing Fan el al., "Adaptive responses to mTOR gene targeting in hematopoietic stem cells reveal a proliferative mechanism evasive to mTOR inhibition," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.2020102118

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