

Study Suggests Anti-Cancer Properties for Diabetes Drug

Metformin Appears More Effective than Other mTOR Inhibitors in Pancreatic Cancer Model



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A new study by a UCLA Division of Digestive Diseases and CURE: Digestive Diseases Research Center team headed by Dr. Enrique Rozengurt provides further evidence that metformin, a front-line drug for the treatment of type 2 diabetes, has anti-cancer properties.

It's well recognized that normal cells become cancerous through a series of steps resulting in the continuous activity of a signaling pathway that stimulates their multiplication and dissemination to other sites. Researchers have focused on identifying drugs that target these dysregulated pathways in an effort to restore normalcy, halting the proliferation of cancer cells. One pathway that has become the subject of growing interest because of its central role in the development of many cancers is mammalian target of rapamycin (mTOR).

Recently there has been a concerted effort in the pharmaceutical industry to move mTOR inhibitors – first rapamycin, and now a second generation of drugs – to the clinic as a potential treatment for certain cancers. But these compounds, while successful at inhibiting the mTOR pathway, have shown limited therapeutic benefits. Rapamycin was found to be an incomplete inhibitor of the pathway. The second-generation inhibitors are more effective in blocking the pathway, but they have their own shortcomings. The reasons for these limitations were explored in a paper by Dr. Rozengurt's group that appears in the journal PLoS ONE.

Working with pancreatic cancer cells, Dr. Rozengurt and colleagues followed up on previous work showing that the new mTOR-inhibiting drugs turn on other pathways involved in cancer, counterbalancing the inhibitory effects. "mTOR drives cell proliferation through insulin and other growth factors, but it also has a regulatory feedback mechanism," explains Dr. Rozengurt, professor of medicine in the Division of Digestive Diseases, director of the CURE: Digestive Diseases Research Center and Hirshberg Professor in Pancreatic Cancer Research. "In addition to sending stimulatory signals to the cell, it moderates the intensity of the growth factors. As a result, by suppressing the growth-promoting effects, you also suppress these moderating effects, which has the unintended consequence of overactivating pathways upstream of mTOR."

Dr. Rozengurt's group found that mTOR inhibitors activate a pathway called MEK/ERK that is linked to Ras – the most commonly activated oncogene in pancreatic cancer. "We know there are very good inhibitors for the MEK/ERK pathway," says Dr. Rozengurt. "What this means is that the future may lie in rational new combinations of drugs to inhibit mTOR and MEK/ERK."

The researchers also examined the impact of an existing drug, metformin, on the MEK/ERK pathway. Metformin is the most common drug used in the control of type 2 diabetes. A series of recent reports, including a set of papers from Dr. Rozengurt's team, indicates that the drug also exerts anti-cancer effects. This is believed to be at least partly due to its ability to efficiently block mTOR, albeit through different mechanisms than rapamycin and the second-generation mTOR inhibitors. "The question became, what are the consequences of metformin's blocking of mTOR – whether it turns on the same feedback loops and shows the same patterns as the other inhibitors," explains Dr. Rozengurt. What his team found was significant: Metformin not only inhibits mTOR in pancreatic cancer cells, but it also suppresses the MEK/ERK pathway – just the opposite of the other mTOR inhibitors.

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Could metformin, when used for patients with type 2 diabetes, be providing the unintended therapeutic benefit of reducing the risk of pancreatic cancer? Given the epidemic of type 2 diabetes in the United States, millions of people have used the drug, providing fertile ground to mine epidemiological data in search of the answer. Sure enough, several groups from different institutions found that people with type 2 diabetes who were treated with metformin showed a reduced susceptibility to pancreatic cancer.

Paired with the laboratory findings of Dr. Rozengurt's group, and consistent with other studies in the field this observational evidence paves the way toward clinical studies, some of them already underway to determine the potential efficacy of metformin, perhaps in combination with other drugs, in pancreatic cancer patients. "If our new findings with cells in culture can be extended to cancer cells in tumors, the results could explain important aspects of the anti-cancer activity of different drugs that target mTOR – and, most excitingly, might suggest the use of rational drug combinations to combat pancreatic cancer in the future," Dr. Rozengurt says.

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"There have been many efforts made to bring mTOR inhibitors to cancer patients, but they have been less than successful because of an unintended consequence — they over-activate other pathways," Dr. Rozengurt concludes. "Now we have this drug, metformin, that has been used in millions of people with type 2 diabetes. It's an old drug that we know a lot about, so if it turns out to be effective in cancer, that will be extremely exciting."