Study questions anti-cancer mechanisms of drug tested in clinical trials

13 January 2014

The diabetes drug metformin is also being tested in numerous clinical trials for treating different cancers, and several studies point to its apparent activation of a molecular regulator of cell metabolism called AMPK to suppress tumor growth.

But new research appearing the week of Jan. 13 in *Proceedings of the National Academy of Sciences* (*PNAS*) suggests that activation of AMPK may actually fuel cancer growth. Researchers from Cincinnati Children's Hospital Medical Center who led the study also recommend that clinicians testing metformin for cancer treatment consider a careful re-evaluation of their clinical data.

The researchers report on extensive laboratory tests that conclude metformin does stop cancer, although not by activating AMPK. Instead, in tests involving glioma brain cancer cells, the authors found that metformin inhibits a different molecule called mammalian target of rapamycin (mTOR) that has been linked to many other cancers.

In the body, metformin also suppresses the actions of insulin and insulin-like growth factors – two molecules that support cancer growth – and also likely independent of AMPK, according to Biplab Dasgupta, PhD, principal investigator and a researcher in the Division of Hematology/Oncology at Cincinnati Children's.

"Our findings do not suggest that clinical trials using metformin should be stopped. Metformin appears to be a very useful drug, but the drug's mechanism of cancer suppression is not clear," Dr. Dasgupta said. "However, our findings unveil a potential role for AMPK as a tumor growth supporter, not a suppressor, in the type of cancer that we study. This is why clinicians using metformin in clinical trials should use caution during data interpretation."

Dasgupta and his research colleagues decided to tackle the question of metformin's anti-cancer properties because some studies point to AMPK as a tumor suppressor, while others have suggested it can promote tumor growth. Ultimately, an accurate understanding of AMPK's role – and how a drug like metformin does stop cancer – will likely be important to continued improvement of targeted cancer therapies, he said.

AMPK is a metabolic enzyme that acts as a key sensor of energy levels in cells. It controls a number of metabolic pathways that allow cells to regulate their energy usage and survival under physiological stress. Cancer cells modify their metabolism to maintain their growth and survival in the stressful environment of the tumor.

To determine how AMPK and metformin react in the context of cancer, the researchers conducted tests using glioblastoma, a highly lethal brain cancer with no cure. Their experiments involved laboratory cell cultures of human glioblastoma cells and glioblastoma tumors transplanted in mice to obtain results in a living organism.

Compared to normal human and mouse tissue, the researchers found that AMPK was highly active in human and mouse glioblastoma cells. This led them to question whether the anti-cancer properties of metformin were independent of AMPK, and instead directed to other molecular pathways.

The researchers then treated human glioblastoma cells with metformin and conducted a series of genetic tests to determine the molecular pathways it uses to stop the cancer growth. Those tests showed clearly that metformin directly inhibited the mTOR pathway (and the cancer) by promoting the interaction of two upstream molecules that stop the pathway's function.

To further verify that AMPK activation by metformin is not involved in stopping the growth of cancer, the researchers also treated the glioblastoma cells with

a more specific AMPK activating compound called A769662 that directly binds to AMPK. The treatment did not kill glioblastoma cells, according to the authors.

Dasgupta and his colleagues are continuing their research by testing direct genetic inhibition of AMPK to see how it impacts human glioblastoma cells. Although that research still has to be completed and the results verified, he said preliminary indications are that blocking AMPK appears to kill a significant number of the glioblastoma cells.

More information: Discrete mechanisms of mTOR and cell cycle regulation by AMPK agonists independent of AMPK , www.pnas.org/cgi/doi/10.1073/pnas.1311121111

Provided by Cincinnati Children's Hospital Medical Center