New combined treatment shows promise in hepatocellular carcinoma

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Dr. Veiga & Dr. Kozma. Credit: IDIBELL

Researchers from the Metabolism and Cancer group at the Bellvitge

Biomedical Research Institute (IDIBELL), led by Dr. Sara Kozma, have unveiled a new potential combined treatment for hepatocellular carcinoma (HCC), the second cause of cancer mortality worldwide. The combination of mTOR inhibitors together with the mitochondrial inhibitor phenformin has shown positive results in in vitro HCC cells, leading to a striking increase in the overall survival of tumor-bearing mice. The study has been reported in *Clinical Cancer Research*.

"Currently available therapeutic options for HCC are very limited and offer poor outcomes, prompting the search for new therapeutic approaches," explains Dr. Kozma, last author of the article. "Inhibitors of the mTOR pathway had already been explored as an alternative treatment, given that this pathway is hyperactivated in most HCCs, but they showed little clinical efficacy. However, as recent data suggested that mTOR inhibitors may promote cancer cell survival by maintaining mitochondrial oxidation and/or autophagy, we set out to examine their use combined with inhibitors of mitochondrial activity."

In their study, researchers show that treatment of HCC cells in vitro with phenformin, a mitochondrial complex I inhibitor, causes a metabolic shift to glycolysis, mitochondrial dysfunction and fragmentation. "These changes sensitize orthotopic liver tumors in mice to dual inhibition of mTOR, which improves tumor-bearing mice overall survival," says Dr. Sonia Veiga, first author of the *Clinical Cancer Research* paper.

"Given the recent approval of phenformin in a clinical trial for melanoma, it will be exciting to explore this regimen clinically in HCC," says Dr. Kozma. According to Dr. Veiga, next steps include testing this combination in human samples thanks to collaboration with Bellvitge University Hospital and the Catalan Institute of Oncology, as well as comparing the results obtained with those of current treatments for HCC.

More information: Sónia R. Veiga et al, Phenformin-Induced Mitochondrial Dysfunction Sensitizes Hepatocellular Carcinoma for Dual Inhibition of mTOR, *Clinical Cancer Research* (2018). DOI: 10.1158/1078-0432.CCR-18-0177