Metformin treatment caused cancer stem cell death in pancreatic cancer cell lines

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Results of some preclinical trials have shown that low doses of the antidiabetic drug metformin may effectively destroy cancer stem cells, a group of cells that are considered to be responsible for tumor initiation and, because they are resistant to standard chemotherapies, tumor relapse.

In addition, when metformin was combined with a standard chemotherapy used for pancreatic cancer, the combination treatment was able to efficiently eradicate both cancer stem cells and more differentiated cancer cells, which form the bulk of the tumor, according to data presented by Christopher Heeschen, M.D., Ph.D., at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, held in Lake Tahoe, Nev., from June 18-21, 2012. Heeschen is professor for experimental medicine at the Spanish National Cancer Research Centre in Madrid, Spain.

Most clinical trials of pancreatic cancer conducted during the last 15 years have failed to show marked improvement in median survival, suggesting that the selected approaches were not sufficient for several reasons, according to Heeschen. In recent years, researchers have identified cancer stem cells which, as opposed to the cancer cells that make up the bulk of the tumor, are a small subset of cells that are resistant to conventional therapy.

"Therefore, efficiently targeting these cells will be crucial for achieving higher cure rates in patients with pancreatic cancer," he said. "Our newly

emerging data now indicate that metformin, a widely used and well-tolerated drug for the treatment of diabetes, is capable of efficiently eliminating these cells."

Specifically, the researchers found that metformin-pretreated cancer stem cells were particularly sensitive to alterations to their metabolism through the activation of AMPK. In fact, metformin treatment resulted in the death of cancer stem cells. In contrast, treatment of more differentiated cancer cells with metformin only arrested the cells' growth.

"As the cancer stem cells represent the root of pancreatic cancer, their extinction by reprogramming their metabolism with metformin in combination with the stalling of the proliferation of more differentiated cells should result in tumor regression and long-term, progression-free survival," Heeschen said.

The researchers generated data to support this idea when they treated immunocompromised mice implanted with a diverse set of patient-derived tumors with a combination of metformin and gemcitabine, the standard chemotherapeutic treatment for pancreatic cancer. They found that the treatment resulted in reduced tumor burden and the prevention of relapse as compared with treatment with either drug alone.

"Intriguingly, in all tumors treated with metformin to date, relapse of disease was efficiently prevented and there were no noticeable adverse effects," Heeschen said.

He believes that testing metformin in pancreatic cancer is ready for clinical trials. The pancreatic research team is currently awaiting results of a study that tested metformin as a maintenance treatment in patients with advanced pancreatic cancer. Although the rationale for this study was based on retrospective data, Heeschen said given these new results

he hopes that this treatment strategy would be highly efficacious.

"Pending the results of this study, an important aspect for the future will be to investigate if all patients respond to metformin or whether some patients, due to distinct genetic alterations, may not respond to this metabolic reprogramming," he said.

More information:

Abstract

Metformin targets human pancreatic cancer stem cells in preclinical mouse models. Enza Lonardo, Michele Cioffi, Yolanda Sanchez, Jorge Dorado, Christopher Heeschen. Spanish National Cancer Research Centre, Madrid, Madrid, Spain.

Pancreatic ductal adenocarcinomas contain a subset of exclusively tumorigenic cancer stem cells (CSCs), which are capable of repopulating the entire heterogeneous populations of cancer cells in the tumor and, even more importantly, are highly resistant to standard chemotherapy. Therefore, the identification of drugs that are capable of selectively targeting CSCs is urgently needed. Here, we demonstrate that low dose metformin, a widely used anti-diabetic drug with an exceptional safety profile, selectively targets freshly isolated human pancreatic CSCs. Specifically, metformin pretreated sphere-derived CSCs showed strong activation of AMPK and loss of expression of pluripotency-associated genes and CSC-associated surface markers. Consecutively, the ability of pretreated CSCs to clonally expand in vitro and in vivo was virtually abrogated, while non-CSCs remained mostly unaffected by metformin treatment. Importantly, induction of energetic crisis resulting in enhanced apoptosis was restricted to p53-deficient CSCs, while p53 wild-type CSCs were resistant to the effects of metformin. Intriguingly, the combination of metformin with gemcitabine, the standard

chemotherapeutic agent for pancreatic cancer, efficiently erased both CSCs and non-CSCs. Finally, in primary tissue xenograft mouse models this combination treatment effectively reduced tumor burden and prevented relapse as compared to either drug alone. Therefore, these data provide a strong experimental basis for further evaluating the combination of metformin and chemotherapeutic drugs to eventually improve the poor prognosis of patients with pancreatic cancer.

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