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Mitochondrial uncoupling protein 2 and pancreatic cancer: A new potential target therapy

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Onconase induces autophagy sensitizing pancreatic cancer cells to gemcitabine and activates Akt/mTOR pathway in a ROS-dependent manner.

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Abstract

Onconase® (ONC) is a member of the RNase super-family that is secreted in oocytes and early embryos of Rana pipiens. Over the last years, research interest about this small and basic frog RNase, also called ranpirnase, constantly increased because of its high cytotoxicity and anticancer properties. Onconase is currently used in clinical trials for cancer therapy; however, the precise mechanisms determining cytotoxicity in cancer cells have not yet been fully investigated. In the present manuscript, we evaluate the antitumoral property of onconase in pancreatic adenocarcinoma cells and in non-tumorigenic cells as a control. We demonstrate that ONC stimulates a strong antiproliferative and proapoptotic effect in cancer cells by reporting for the first time that ONC triggers Beclin1-mediated autophagic cancer cell death. In addition, ONC inhibits the expression of mitochondrial uncoupling protein 2 (UCP2) and of manganese-dependent superoxide dismutase (MnSOD) triggering mitochondrial superoxide ion production. ONC-induced reactive oxygen species (ROS) are responsible for Akt/mTOR pathway stimulation determining the sensitivity of cancer cells to mTOR inhibitors and lessening autophagic stimulation. This indicates ROS/Akt/mTOR axis as a strategy adopted by cancer cells to reduce ONC-mediated cytotoxic autophagy stimulation. In addition, we demonstrate that ONC can sensitize pancreatic cancer cells to the standard chemotherapeutic agent gemcitabine allowing a reduction of drug concentration when used in combination settings, thus suggesting a lowering of chemotherapy-related side effects. Altogether, our results shed more light on the mechanisms lying at the basis of ONC antiproliferative effect in cancer cells and support its potential use to develop new anticancer strategies.

KEYWORDS: autophagy; gemcitabine; mammalian target of rapamycin (mTOR); onconase; pancreatic cancer; reactive oxygen species (ROS)

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