AB079. P051. Blockage of CTR1-dependent copper absorption increases autophagy to resist apoptosis of pancreatic ductal carcinoma cells

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Abstract: Clinical observations have demonstrated that copper levels elevate in a number of cancer types, and copper deprivation is considered a prospective anti-cancer therapeutic strategy. However, the cellular mechanism underlying copper depletion in cancer therapy is still not fully understood. Here, we demonstrate that CTR1-dependent copper level is negatively correlated with the survival time of pancreatic ductal carcinoma patients and copper increase is important for pancreatic ductal adenocarcinoma progression. However, copper depletion via CTR1 knockdown or copper chelation did not induce pancreatic cancer cell apoptosis. We found that copper deprivation causes increased ROS and decreased ATP, which rendered cancer cells in a dormant state. Strikingly, copper deprivation caused an increase in autophagy to resist apoptosis of pancreatic cancer cells. Simultaneous treatment with copper chelator tetrathiomolybdate (TM) and autophagy inhibitor chloroquine diphosphate salt (CQ) increased apoptotic cancer cells in vitro and retarded cancer growth in xenotrans planted mice. These findings reveal that copper deprivation-caused cell dormancy and an increase in autophagy is a major reason for the poor clinical outcome obtained from copper depletion therapies for cancers. Therefore, the combination of autophagy inhibition and copper depletion is potentially a novel strategy for the treatment of pancreatic cancer and other copper-dependent malignant tumours.

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