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Autophagy Inhibition Induces Apoptosis on Low-Grade Pancreatic Neuroendocrine Tumor Mouse Model

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BACKGROUND: Autophagy is an intrinsic pathway through which cells digest organelles or foreign proteins to supply amino acids. Autophagy inhibition has been shown inhibitory effect on cancer cells, and clinical trials using autophagy inhibitor chloroquine (CQ) or hydroxychloroquine (HCQ) are ongoing in several cancers. The aim of this study is to investigate the mechanism how CQ induces apoptosis on PanNET cell lines and to test whether HCQ shows inhibitory effect on PanNET models in vivo.

METHODS: PanNET cell lines MIN6 and QGP-1 were used. Genetically engineered mice with heterozygous mutation in Men1 gene (Men1+/ΔN3-8) were bred for 18 months and then HCQ 10 mg/kg or saline was intraperitoneally administered for 21 consecutive days. On day 22, mice were sacrificed and whole pancreas were sectioned and histologically analyzed.

RESULTS: CQ treatment resulted in reduced proliferation and apoptosis induction on both PanNET cell lines. With CQ treatment, endoplasmic reticulum (ER) stress was induced and unfolded protein response was activated through the PERK-eIF2α-ATF4 pathway resulting in the expression of pro-apoptotic protein CHOP, indicating the ER stress-mediated apoptotic cell death. 18-month-old Men1+/ΔN3-8 mice had pancreatic tumors with low Ki-67 labeling indexes. HCQ administration decreased mean tumor size, but there was no significant change in the number of tumor or Ki-67 labeling index. Histological analyses showed more TUNEL positive apoptotic cells and more CHOP positive cells in HCQ group.

CONCLUSION: Autophagy inhibition induced apoptosis on PanNET cell lines and Men1+/ΔN3-8mouse PanNET model. Inhibitory effect of HCQ might be beneficial on PanNET patients.