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HSF1 inhibition sensitizes pancreatic cancer to Gemcitabine via the suppression of cancer stem cell-like properties

Pancreatic cancer is a fatal disease with poor prognosis. Gemcitabine has been regarded as the mainstay of chemotherapy for pancreatic cancer; however, it is accompanied with a high rate of chemoresistance. We have previously reported that heat shock factor 1 (HSF1) is involved in the invasion and metastasis of pancreatic cancer, a highly conserved transcriptional factor that mediates the canonical proteotoxic stress response. Here, we further investigate whether HSF1 contributes to the chemoresistance of pancreatic cancer cells caused by gemcitabine and to explore the underlying mechanisms. Genetically engineered mice (LSL-KrasG12D/+; Trp53fl/+; Pdx1-Cre mice), which spontaneously develop pancreatic cancer, were used to examine the sensitivity of pancreatic cancer to gemcitabine *in vivo*. Sphere formation assays were employed to assess the tumor sphere-forming ability of pancreatic cancer cells. The expression of cancer stem cell (CSC)-associated markers was determined by Western blotting and quantitative real-time PCR. Small interfering RNA targeting HSF1 was used to down-regulate the expression of HSF1. MTT assays were performed to determine the sensitivity of pancreatic cancer cells to gemcitabine. We found that HSF1 was enriched in sphere-forming cancer cells. Panc-1 and MiaPaCa-2 cells treated chronically with gemcitabine displayed increased transcription and expression of CSC-associated markers. In addition, gemcitabine-surviving Panc-1 and MiaPaCa-2 cells showed an increased ability to form tumor spheres. Moreover, we observed that gemcitabine treatment increased the activity and expression of HSF1, as well as transcription of its downstream targets. Finally, HSF1 inhibition significantly suppressed the expression of CSC-associated markers, augmented the cancer-killing property of gemcitabine, and increased chemosensitivity to gemcitabine *in vivo*. Our study reveals a novel mechanism in which HSF1 promotes the chemoresistance of pancreatic cancer to gemcitabine by modulating CSC-like properties. Targeting HSF1 could be thus a rational strategy to improve treatment outcomes.

Recent Publications

1. Guo K, Ma Q and Xie K (2017) A novel KLF4-MSI2 signaling pathway regulates growth and metastasis of pancreatic cancer. Clin Cancer Res 23(3):687-696.
2. Chen K, Qian W and Ma Q (2017) Metformin suppresses cancer initiation and progression in genetic mouse models of pancreatic cancer. Mol Cancer 16(1):131.
3. Zong L, Chen K, Ma Q and Wang Z (2017) Lipoxin A4 reverses mesenchymal phenotypes to attenuate invasion and metastasis via the inhibition of autocrine TGF-β1 signaling in pancreatic cancer. J Exp Clin Cancer Res 36(1):181.
4. Jiang Z, Zhou C, Ma Q and Ma J (2018) Inhibiting YAP expression suppresses pancreatic cancer progression by disrupting tumor-stromal interactions. J Exp Clin Cancer Res 37(1):69.

5. Cao J, Li J, Sun L and Ma Q (2018) Hypoxia-driven paracrine osteopontin/integrin αvβ3 signaling promotes pancreatic cancer cell epithelial-mesenchymal transition and cancer stem cell-like properties by modulating FOXM1. Mol Oncol. 13(2):228-245.

Biography

Qingyong Ma has his expertise in pancreatic cancer for both scientific research and clinical studies. He has published more than 150 papers in reputed journals and has been serving as an Editorial Board Member of reputed journals. He has completed his PhD from Queen's University of Belfast during 1992 to 1996. He is the Professor and Head of the Department of Surgery, First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, and China.

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