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Wen-Jing Liu^{1#}, Jun Lu^{1#}, Wei-Xun Zhou², Jian-Zhou Liu¹ and Li Zhou¹

¹Department of General Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing 100730, China.

²Department of Pathology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing 100730, China.

MLH1 Inhibits Metastatic Potential of Pancreatic Ductal Adenocarcinoma via Downregulation of GPRC5C

Abstract:

DNA mismatch repair gene MutL homolog-1 (MLH1) has divergent effects in many cancers; however, its impact on the metastasis of pancreatic ductal adenocarcinoma (PDAC) remains unclear. In this study, MLH1 stably overexpressed (OE) and knocked down (KD) sublines were established. Wound healing and transwell assays were used to evaluate cell migration/invasion. In vivo metastasis was investigated in orthotopic implantation models (severe combined immunodeficiency mice). RT-qPCR and western blotting were adopted to show gene/protein expression. MLH1 downstream genes were screened by transcriptome sequencing. Tissue microarray-based immunohistochemistry was applied to determine protein expression in human specimens. In successfully generated sublines, OE cells presented weaker migration/invasion abilities, compared with controls, whereas in KD cells, these abilities were significantly stronger. The metastasis-inhibitory effect of MLH1 was also observed in mice. Mechanistically, G protein-coupled receptor, family C, group 5, member C (GPRC5C) was a key downstream gene of MLH1 in PDAC cells. Subsequently, transient GPRC5C silencing effectively inhibited cell migration/invasion and remarkably reversed the proinvasive effect of MLH1 knockdown in KD cells. In animal models and human PDAC tissues, tumoral GPRC5C expression, negatively associated with MLH1 expressions, was positively correlated with histologic grade, vessel invasion, and poor cancer-specific survival. In conclusion, MLH1 inhibits the metastatic potential of PDAC via downregulation of GPRC5C.

Keywords: GPRC5C; MLH1; metastatic potential; pancreatic ductal adenocarcinoma; prognosis.

Biography :

Surgical treatment of hepatobiliary and pancreatic diseases Clinical, basic and translational research on pancreatic diseases (pancreatic cancer, pancreatic neuroendocrine tumors, pancreatic cystic tumors, pancreatitis, minimally invasive pancreatic surgery, islet transplantation, immunotherapy, etc.). Major: General Surgery.

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