MPZL1 promotes gastric cancer metastasis and chemoresistance through PARP1 and CHK2 signalings

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BACKGROUND: Gastric cancer is one of the most common causes leading to cancer-related death in China. Chemoresistance and distant metastasis are the major reasons. The tyrosine phosphatase PTPN11/SHP2 is associated with tumor development in many cancers. However, the function of their substrate MPZL1 in human cancers is elusive. In this study, we investigated the role of MPZL1 in gastric cancer metastasis and chemoresistance.

HYPOTHESIS: Human gastric cancer cell lines AGS, GTL16, SNU216, and SGC7901 were used to investigate cell proliferation, migration, invasion, colony formation, apoptosis, and tumorigenesis by CCK8, scratch-wound, transwell, plate clone, flow cytometery, and animal models after MPZL1 or its associated proteins were over-expressed or silenced. Protein expression in cell lines and tissues was examined by either Western blot, immunofluorescence, or immunohistochemical staining.

METHODS: Overexpression of MPZL1 promoted cell proliferation, migration, invasion, tumor formation, and metastasis, but silence of MPZL1 inhibited those activities. In addition, SGC7901/MPZL1 and SNU216/MPZL1 were resistant to 5-fluorouracil and cisplatin chemotherapy, and knock down of MPZL1 in AGS and GTL16 showed enhanced chemosentivity. Further mechanism studies revealed that MPZL1 increased the expression of PARP-1 (Poly (ADP-ribose) polymerase-1) and pCHK2 to promote gastric cancer metastasis and chemoresistance, which could be inversed by knock down of MPZL1, CHK2 inhibitor or Parp1 inhibitor. Kaplan-Meier analysis of 112 gastric cancer patients showed that over-expression of MPZL1 correlated with poor overall survival (P = 0.006) and disease-free survival (P=0.034).

RESULTS: Our results suggest that MPZL1 promotes gastric cancer metastasis and chemoresistance through regulating PARP1 and pCHK2. Thus, perturbing synergistically MPZL1 and PARP1 signaling may offer a new therapeutic approach to treat gastric cancer patients, especially those with metastasis and chemoresistance.