

Title: Midkine (MK) promotes perineural invasion in human pancreatic cancer

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) The authors claim that MK is predominantly expressed by cancer cells, whereas according to figure 1C and D, the stained cells are mainly stromal cells featured by spindle shape and/or Low nucleus/cytoplasm ratio.

Answer: Our experiments showed that MK was expressed in the cytoplasm of tumor cells and found predominantly in invasive carcinoma cells. Simultaneously, immunoreactions were also observed in the desmoplastic stromal cells within the tumor mass in MK-positive cases. These stromal cells exhibited spindle shape features and/or low nucleus/cytoplasm ratio. Figure 1D does not represent our experimental results and we have replaced it with another figure.

(2) In this study, MK staining in patient samples was graded into two groups, moderate and intense expression as shown in figure 1C and D respectively. But as far as I am concerned, this evaluation is very subjective. In figure 1D there are more MK positive cells but the MK staining in figure 1C is stronger in each individual cells.

Answer: Our experiments showed that MK staining in high expressing groups is stronger in most individual cells, with more MK positive cells. Figure 1D does not represent our experimental results and we have replaced it with another figure.

(3) Did authors analyze MK and syndecan-3 double positive population for clinicopathological features, perineural invasion, and prognosis?

Answer: We analyzed the patient population that were positive for both MK and

syndecan-3 for clinicopathological features, perineural invasion, and prognosis. High MK expression was associated with lymph nodes metastasis. Syndecan-3 expression was associated with tumor size. However, the coexpression of MK and syndecan-3 in patients positive for both biomarkers did not correlate with any clinicopathological features. Perineural invasion in patients positive for MK and syndecan-3 were significantly higher than in those patients that did not express these biomarkers. Coexpression of MK and syndecan-3 did not also associate with prognosis, or as independent prognostic factors of overall survival.

(4) Minor points: -section Methods-patient specimens, page 6: histological grading is not well reported. - 5 patients with stage IV cancer underwent pancreaticoduodenectomy. This is not so frequent: please discuss this point.

Answer: histological grading is : grade I :well differentiated; grade II :moderately differentiated; grade III:poorly differentiated and undifferentiated.

Only the right lobes isolated from 5 patients with stage IV metastatic cancer underwent pancreaticoduodenectomy. The tumor sizes ranged from a diameter of 2-4cm. Three patients had radiofrequency ablation treatment before surgery, and two patients exhibited metastases in the liver edge and underwent local excision surgery.

(5) For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies.

Answer: I have provided language certificate by professional English language editing companies.

(6) The data has been appear in the text. It's seemed redundant using a table. Would you please omit this table?

Answer: Table 2 has been omitted from the manuscript, and Table 3 has been changed to Table 2.

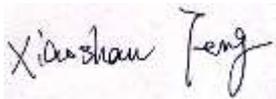
(7) Would you please provide the decomposable figure of Fiugres, whose parts are movable and words can be edited.

Answer: The original pictures are provided as words and can be easily edited.

3 References and typesetting were corrected

Thank you again for your consideration of our manuscript for World Journal of Gastroenterology.

Sincerely yours,

A handwritten signature in black ink that reads "Xiaoshan Feng". The signature is written in a cursive style and is placed on a light pink rectangular background.

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