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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5595
Title: Midkine (MK) promotes perineural invasion in human pancreatic cancer
Reviewer code: 00037961
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-09-16 17:27
Date reviewed: 2013-09-19 04:40

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

The purpose of this study is to determine whether or not, midkine (MK), a heparin-binding growth factor,also known as neurite growth promoting factor and its receptor syndecan-3 may play an important role in the perineural invasion and prognosis of human pancreatic cancer. In this study, MK and syndecan-3 proteins levels in 42 patients with pancreatic cancer were detected by immunohistochemistry and analyzed for clinicopathological features, perineural invasion, and prognosis. Results: MK and syndecan-3 were found in 26 (61.9%) and 24 (57.1%) specimens, respectively. MK and syndecan-3 expression were associated with perineural invasion (P = 0.018 and P =0.031, respectively). High MK expression was closely associated to advanced TNM stage (P = 0.008), lymph node metastasis (P = 0.042), and decreased postoperative survival at 3 years (51.0% vs 21.8%, P = 0.001). Syndecan-3 levels also correlated with tumor size (P = 0.028) and patients who were syndecan-3 negative had a higher cumulative survival rate than those who were positive. Conclusions: MK and syndecan-3 in pancreatic cancer are frequently expressed and associated with perineural invasion. High expression of MK combined with syndecan-3 may contribute to the highly perineural invasion and poor prognosis of human pancreatic cancer. Comments: This is an interesting observation in these selected group of patients. However, the patient size in individual groups studied is too small to provide a definitive conclusion and to introduce these procedures in the diagnostic settings. Because of the size of samples one cannot randomize these patients. The quantitation of the H and E stained slides are unclear.The observations are clear but gross. It was also not clear whether or not the observations by pathologists are blinded. The study, however provide another approach in our understanding of gradation of pancreatic cancer with this approach. Can this approach be used in pre-cancerous state? It would be nice if the authors can provide a cost

analysis and time frame required for the determination of these measurements in order to use this approach as diagnostic criteria.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

In this paper, the Authors evaluated the role of Midkine (MK), a heparin-binding growth factor, and Syndecan-3, a high affinity receptor for MK, in the perineural invasion and prognosis of pancreatic cancer. MK and Syndecan-3 in 42 patients with pancreatic adenocarcinoma were detected by immunohistochemistry and analyzed for clinicopathologic features , perineural invasion, and prognosis.Results showed that MK and Syndecan-3 are frequently expressed in pancreatic cancer and associated with perineural invasion: these findings contribute to the highly perineural invasion and poor prognosis of ductal adenocarcinoma of the pancreas. The number of cases included is small but the evidence of such expression of neurite growth-promoting factors in pancreatic cancer is interesting. However, the clinical implication of these features is difficult to try, since MK and Syndecan-3 expression were not independent prognostic factors. Perhaps, the detection of MK and Syndecan-3 may be useful in precancerous lesions or in preoperative aspirated biopsy, when the prognosis is important for appropriate management. 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.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

In this manuscript, the authors provided some data on the relevance between expression of midkine and its receptor syndecan-3 and some clinical features in pancreatic cancer patients. While the data are interesting, there are still some concerns that need attention. Specific Comments: 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. So in order to confirm this, they can further check the co-localization of MK with K19 (tumor marker) using immunofluorescence. 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. So I suggest the authors applying more objective scoring methods or not scoring at all. 3. Did authors analyze MK and syndecan-3 double positive population for clinicopathological features, perineural invasion, and prognosis?