Reviewer's report

Title: High expression of P21-activated protein kinase 1 is an independent prognostic factor in primary and metastatic pancreatic cancer

Version: 2 Date: 26 April 2014

Reviewer: Takeo Shimasaki

Reviewer's report:

Juan Han et al. examined the expression of the p21-activated protein kinase 1 in pancreatic cancer samples and liver metastatic tissue of patients with a histopathological diagnosis of pancreatic cancer. These authors found a correlation between PAK1 protein expression and age as well as PAK1 protein expression and histopathological differentiation. These results are interesting. The authors also insist that PAK1 is a novel prognostic marker, namely, that high PAK1 expression predicts better overall survival compared to low expression. Nevertheless, the authors need to address the following issues that weaken the rigor and significance of the study.

Major comments

1. This paper shows good experimental work, but statistical analysis is inadequate. The method and results of multivariate analysis in relation to a confounder are not described well enough. Because the expression of PAK1 correlates with a histological type, the exclusion of the confounder is an important point to consider during validation of an independent prognostic factor. The situation is similar with clinical staging. If the authors insist on it, they have to at least prove that PAK1 is an independent factor regardless of a clinical stage and the degree of differentiation. (Please see specific comment 1)

2. There are no data on the expression of PAK1 in the liver metastatic tissue and during pathological differentiation. Contrary to previous reports, the authors state that PAK1 expression is higher in primary pancreatic cancer tissues than in metastatic tissues. In contrast, this manuscript lacks the data on the number of metastatic pancreatic cancer patients according to histopathological differentiation. Without the detailed data on metastatic pancreatic cancer, referees and readers could not understand the title.

3. This PAK1 expression in the metastatic tissue can be under the influence of differentiation and metastatic signs during diagnosis. I cannot understand and agree with the results without data on histopathological differentiation and clinical outcomes. In particular, to describe the relationship of metastasis with PAK1, the authors should describe the clinical definitive outcome of the metastasis. The samples and clinical data are usually collected and analyzed at the point of diagnosis. When cancer progression is observed after treatment, histological studies are generally not performed. I think that these data from histological
evaluation, which are suggestive of metastatic tissue, should not be analyzed only in metastatic cases at an early stage of clinical course. It is not appropriate to search for correlations between PAK1 expression and the presence of metastases at diagnosis. Furthermore, we cannot rule out the possibility that the results will change if the metastatic cases are added to the middle and the end of the clinical course. If the authors would like to discuss the metastasis and PAK1, they should compare PAK1 expression in a primary pancreatic cancer with or without a definitive metastasis. As mentioned above, there are no data in this manuscript that supports the statement in the title.

Specific comments

1. The running title appears awkward in the present manuscript. One of the alternatives may be “Reduced expression of p21-activated protein kinase 1 correlates with poor histological differentiation in pancreatic cancer.” If the authors could demonstrate additional statistical data (i.e., a Kaplan–Mayer survival curve according to the degree of differentiation and clinical stages I, II, III, and IV and the results of statistical analysis), then I would agree with the phrase “an independent prognostic factor.”

2. Clinical and histopathological evaluation of metastatic cancer should be shown in a new table along with the number of cases, if the authors would like to include the data on metastatic pancreatic cancer.

3. The authors need to provide a detailed description of the statistical method of the multivariate analysis with adjustment factors.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests