Reviewer's report

Title: Y-box protein-1/p18 fragment identifies malignancies in patients with chronic liver disease

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Reviewer: Joerg Schrader

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Review
Tacke and Kanig et al. “Y-box protein-1/p18 fragment identifies malignancies in patients with chronic liver disease”

Tacke and Kanig et al. describe a novel fragment of the cold-shock protein YB-1 in the plasma of patients with malignancies. The identified a 18kDa fragment of YB-1 by Western Blot in the plasma of patients with various solid organ cancers, which is not present in healthy controls. Acute inflammation or renal impairment does not seem to have an effect on the levels of this fragment in patients, but was detected in 5 out of 60 patients in this group without a known underlying malignant disease. In two different cancer cohorts comprising 25 HCC patients and 20 metastatic cancer patients of various primary origin the specific 18kDa fragment could be detected in 44% and 80% respectively. They went on to evaluate this fragment as a screening tumour marker for malignant disease in 111 patients undergoing extensive search for non-detected tumour diseases in the process of evaluation for liver transplantation. Here 6 patients with detected cancer were positive for the YB-1/p18 fragment, whereas the same number of detected cancers were positive for the established HCC tumour marker AFP.

Overall this study is interesting and novel and the identified protein fragment has the potential to become a new tumour marker. Nevertheless, a few points remain unclear and need attention.

Major Compulsory Revisions

1. Although the authors evaluated the presence of the p18 fragment of YB-1 protein with different antibodies a formal proof of identity would be helpful. If any of the antibodies would work on immunoprecipitation a mass spectometry analysis would be the method of choice – otherwise a preabsorption of the antibody with recombinant protein or corresponding peptides would be an alternative. In due course it seems puzzling, that the preparation of recombinant protein contains the p18 fragment as well – it would be interesting to speculate weather this is a transcriptional variant or a proteolytic fragment?

2. Could the level of the p18 fragment be correlated to the total (full length) YB-1 protein in the same plasma sample?
3. The authors extensively evaluate the prognostic value of YB-1/p18 in the cohort of 111 patients undergoing evaluation for liver transplantation. Although these data are interesting, the low number of positive correlations (only 6 patients YB-1/p18 positive out of 20 patients with detected malignancies) and the high number of negative correlations (14 patients YB-1/p18 positive out of 91 without detected malignancies) warrant a more cautious discussion of these findings. It would be interesting to know how many “newly” diagnosed tumour diseases would have been detected by the use of YB-1/p18 once all patients with a known tumour disease (HCC n=4, liver metastasis n=3) as a reason for liver transplantation were excluded.

Minor Essential Revisions

1. The species source for the recombinant YB-1 gene sequence should be stated.

2. An earlier study has evaluated the prognostic significant of YB-1 positivity in HCC tissue (Yasen et al 2005) – this should be mentioned and included in the references.

3. The second last sentence on page 9 starting “The fastest running band.....” needs to be revised.

4. The statement on page 10, line 4 is difficult to understand, as it currently reads as if the absence of cirrhosis is associated with higher rates of malignancies, which is not true for the frequency of HCC in patients with liver disease.

Discretionary Revisions

1. It would be interesting to speculate on the origin of the p18 fragment in the tumour patients. Does it come from the cancer cells themselves or from infiltrating stromal cells? Is it intra- or extracellularly processed?

2. Is the YB-1/p18 fragment a specific (qualitative) tumour phenomenon, or is it related to the total amount of YB-1 protein produced by the tumour, hence a mere quantitative phenomenon?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.