Reviewer's report

Title: Low expression of the X-linked ribosomal protein S4 in human serous epithelial ovarian cancer is associated with a poor prognosis

Version: 1  Date: 23 November 2012

Reviewer: Erik Wiemer

Reviewer's report:

The authors previously demonstrated an interaction between YB-1 and RPS4X in breast cancer and showed that RPS4X downregulation leads to cisplatin resistance. In the current manuscript RPS4X and YB-1 levels are determined by immunohistochemistry in appr. 200 high grade serous ovarian cancer samples. RPS4X levels - but not YB-1 levels – correlated most importantly to longer overall survival and lower risk of disease progression. These observations suggest that tumors with relatively low levels of RPS4X do worse on the chemotherapy given to ovarian cancer patients. In fact depletion of RPS4X by siRNAs in OVCAR-3 and SK-OV-3 ovarian cancer cell lines causes a clear reduction in growth rate especially in SK-OV-3 and leads to an increased resistance to cisplatin.

Although interesting, a few important issues need to be addressed before this paper can be considered for publication.

Major compulsory revisions

1. Page 4, line 16 – The eligibility criteria are described in the material and method section and state clearly “platinum-based post-operative chemotherapeutic treatment for ovarian cancer” as one of those criteria. In contrast in the discussion section the authors write: “As the immunohistochemistry study was performed on serous high-grade ovarian tumors from patients who had not received chemotherapeutic treatment, low expression of RPS4X could also correlate with intrinsic resistance, although this remains to be determined”. Did the author not adhere to their own eligibility criteria, please explain?

2. How can RPS4X levels be used in the clinic as prognostic marker? Have the authors tried more quantitative ways of measuring RPS4X expression e.g. RT-PCR? Please mention this in the discussion section.

3. The authors present evidence that RPS4X downregulation affects cellular proliferation and confers resistance to cisplatin. Exactly how RPS4X modulates cisplatin sensitivity is not known. In the discussion section (page 11) the authors speculate that the reduced growth rate caused by RPS4X depletion affects the cellular survival after cisplatin exposure. Is the RPS4X mediated resistance phenotype specific for cisplatin or is it a general effect seen with other (DNA damaging) chemotherapeutics as well? The authors should mention this in the discussion.
Minor essential revisions

1. Page 7 – The word sulforhodamine is misspelled multiple times, correct is sulforhodamine.
2. Page 8, line 2 – Line 2 mentions 193 clinical samples whereas Table 1 mentions 196. Please correct.
3. Page 9 – Please include data not shown in a supplemental figure.
4. Page 9, line 26 – Did not detect differences……… What was the rationale behind analyzing p16, p21 and p53 expression? Please include in the text.
5. Page 10, line 1 – Figure 4 should be changed into Figure 5.
6. Table 1 – Explain what censured (censored?) and non-censured (non-censored?) means in the legend.
7. Figure 4 legend – Figure 4 does not show cisplatin resistance data, correct figure title. OVCAR-1 should be OVCAR-3.
8. Figure 5 legend – sulforhodamine should be sulphorhodamine.
9. Is there any information whether the tumors that express relatively low levels of RPS4X grow more slowly than tumors that express high levels of RPS4X?

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

**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