Reviewer's report

Title: Downregulation of SAV1 plays a role in pathogenesis of high-grade clear cell renal cell carcinoma

Version: 1 Date: 14 September 2011

Reviewer: Yoshitaka Sekido

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The authors analyzed 8 RCC cell lines with array CGH and expression analyses and identified chromosome 14q22.1 deletion, where the SAV1 (also called WW45) gene is located. They transduced SAV1 expression vector into a RCC cell line with SAV1 deletion and found that exogenous SAV1 inhibited colony formation of the cells. They also performed a SAV1 knockdown experiment with RNA interference and found that the SAV1 knockdown prompted cell proliferation of two cell lines. Furthermore, they also confirmed that SAV1 inhibited the transcriptional activity of the YAP and TEAD3 complex. Finally, they demonstrated that SAV1 downregulation is frequently observed in most RCC cases immunohistochemically. This well-designed and performed study presents a very convincing data that SAV1 is one of key tumor suppressors of RCC.

Comments

1. In their previous study (Ref 7), the authors showed frequent allelic loss of chromosome 14q in primary RCC samples with array CGH analysis. However, they seemed to cover the 14q22.1 region with 2~3 BAC clones, which might not have been sufficiently sensitive to detect SAV1 deletion. Since the homozygous deletion region at 14q22.1 in the 786-O cells seems very narrow, and seemed detectable with only 2-3 dots on the 44K array (Figure 1S), the previous analysis might have missed such tiny homozygous deletion. They should therefore more vigorously perform quantitative genomic PCR analysis to determine how frequently SAV1 deletion is actually observed in RCC specimens.

2. In relation to comment 1, the authors should perform mutation analysis to determine whether SAV1 can also be inactivated with a missense or nonsense mutation in RCCs. If genomic DNA is not available for all the samples, selected samples with low expression of SAV1 may be sufficient for the analysis.

3. One of the case numbers is #46 in Figure 5 legend, whereas is #96 in Figure 5. Which is correct?

Level of interest: An article of outstanding merit and interest 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.