Reviewer's report

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

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Reviewer: Dae-Sik Lim

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Previously, genes located at 14q with copy number loss seemed to be downregulated in high-grade ccRCC, but putative tumor suppressor genes at this region was not defined. This paper finally showed that SAV1, a component of mammalian Hippo pathway, was down-regulated with copy number loss in high-grade ccRCC. Furthermore, they characterized the proliferation and apoptosis in cells with either Sav1 expression or SAV1 depletion and examined the YAP activity.

Even I did not find further significant advance in understanding the SAV1-mediated Hippo pathway at the molecular level, I think their major finding that SAV1 was down-regulated with copy number loss in high-grade ccRCC is clinically important to understand how Hippo pathway is defective in renal carcinoma. Thus, this MS can be acceptable in BMC cancer after addressing the following raised minor issues.

- Minor Essential Revisions

1. In the second paragraph of Background section (page 5), “~suggesting that 14q loss is important for the development of the latter”, ‘latter’ should be changed as ‘former’ to indicate high-grade ccRCC.

2. In figure 5, the authors should show the specificity of the SAV1 antibodies used and the negative control staining (normal IgGs staining). In fact, I am not sure whether SAV1 antibody specifically recognize SAV1 protein in immunostaining. Thus, the authors should show the reduced levels of SAV1 staining in SAV1-depleted cells or SAV1-null cells and normal staining of SAV1 in control cells expressing SAV1.

3. In second part of the Result section with subtitle “SAV1 inhibits colony formation and cell proliferation”, the authors are overstating some part of the data regarding the effects of SAV1 depletion on cell proliferation. In upper panel of Figure 3b, cell proliferation measured by MTS assay is only slightly increased in siSAV1 clones compared to controls. Furthermore, BrdU ELISA assay in Figure 3B(increased proliferation) and cell cycle analysis in supplementary figure S4(no difference) are not consistent to each other. Thus, downregulation of SAV1 seems to have moderate or mild promotion in cell proliferation rather than significant.
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