Reviewer's report

Title: IQGAP1 and IQGAP2 are Reciprocally Altered in Hepatocellular Carcinoma

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Reviewer: Jun-ichi Okano

Reviewer's report:

White CD et al. investigated the involvement of IQGAP1 and IQGAP2 in the pathogenesis of human hepatocellular carcinoma (HCC) and implied the possibility that these proteins might be utilized in the diagnosis of HCC. Their data are mostly consistent with the theory that IQGAP2 may represent a tumor suppressor and IQGAP1 an oncogene in HCC. However, I have some concerns as below.

<Major Compulsory Revisions>

They examined the expression levels of IQGAP1 and IQGAP2 in normal liver, adenoma, cirrhosis, and HCC. They need to see them in dysplastic nodules, which can be often difficult to differentiate from HCC morphologically. The results may give an answer if IQGAP1 and IQGAP2 can be useful markers in discriminating HCC and dysplastic nodules.

In table 2, although they say that no significant correlation was noted between expression of IQGAP1 or IQGAP2 and any clinical or pathological features, there is no such information in table 1. Expression levels of IQGAP1 and IQGAP2 need to be demonstrated by every parameter, even when there is no significant correlation between them.

They say in discussion that increased IQGAP1 and/or decreased IQGAP2 expression may be a characteristic of a more invasive and metastatic HCC phenotype. This appears to contradict the results of figure 3 showing no correlation between expression levels of IQGAP1 and/or IQGAP2 and tumor stages. How would they compromise with this point?

< Discretionary Revisions>

As they described in the background session, IQGAP1 binds a variety of signaling molecules including Cdc42 and Rac1, ERK and MEK kinases, beta-catenin, E-cadherin, APC, and mTOR. It would be curious to see if these molecules are activated in HCC cells and tissues with high expression levels of IQGAP1. If they could find some of these molecules are simultaneously activated with IQGAP1, this could further clarify the pathogenesis of HCC and could be useful in increasing the accuracy of the diagnosis of HCC.

Best regards,
Jun-ichi Okano, M.D.

**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.