Reviewer’s report

Title: Dietary grape polyphenol resveratrol increases mammary tumor growth and metastasis in immunocompromised mice

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Reviewer: Takako Sakamoto

Reviewer’s report:

(Major Compulsory Revisions)

1. Authors aimed to investigate the effects of a range of dietary concentrations (0.5, 5, 50 mg/kg body weight) of resveratrol on breast cancer as mentioned in Abstract. It seems to be a good point to focus on the dosage of resveratrol. If they state that 0.5, 5, 50 mg/kg body weight dosage is “range of dietary concentrations”, they should refer some papers which indicate they are “range of dietary concentrations” in Background. Alternatively, they may determine the serum levels of resveratrol comparing with those in human.

2. Authors used ERa (-), ERb (+) MDA-MB-231 and ER(-) MDA-MB-435 breast cancer cell lines. ERa, which plays important roles in breast cancer cells, is not expressed in both of these cell lines. They also need to conduct experiments using ERa (+) cell lines, because resveratrol has been reported to possess estrogenic activities.

3. I recommend authors to indicate error bars in Figs.1A and 1D to understand data easily. In addition, they should define “means and standard deviation.” in figure legends of 1A, 1C, 1D, and 1F.

4. I recommend authors to indicate numbers of mice (e.g. 2/12) along with % of mice in Table 1 to understand data easily.

5. Photos of western blotting in Rac should be demonstrated as evidence in Fig.3, like fig.5 in reference 33 which has been reported by authors previously.

6. AKT and JNK are activated when they are phosphorylated. Therefore, activated form of these proteins should be determined along with status independent form of them. Also, photos of western blotting should be demonstrated as evidence in Fig.4.

7. Authors determined only AKT, JNK and PAK protein expressions together with Rac activities. For publication, it is necessary to clarify the molecular mechanisms of enhancement of cancer cell growth and metastasis induced by resveratrol.

8. In previous report by authors (Translational Oncology, 1:19-27, 2008), they demonstrated that resveratrol, even though it was combined with quercetion and catechin, reduced cell proliferation using same cell line and similar mouse model.
They should describe explanations of the discrepancy referring this paper in Results and Discussion.

(Discretionary Revision)

9. Authors state that their results suggest that resveratrol-mediated induction of metastasis might be, at least partly due to increased Rac activity in Results and Discussion, fourth paragraph. To strengthen this study, I recommend authors to conduct experiments using MBA-MB-231 cells stably expression dominant-negative Rac, which they used in reference 33 which has been reported by authors previously.

**Level of interest:** An article of limited interest

**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.