Reviewer's report

Title: Glucose-regulated protein 58 modulates beta-catenin protein stability in cervical adenocarcinoma

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Reviewer: Xianghui Fu

Reviewer's report:

In this manuscript, Liao and colleagues have studied the role of Grp58 and its underlying mechanism in cervical cancer. By analyzing the Affymetrix data from their previous report (Liao et al, Cancer Sci, 2011:2255-63), they found that WNT signaling is significantly disrupted in Grp58 knockdown cells. They further stated that Grp58 regulates beta-catenin protein degradation and knockdown of Grp58 leads to membrane accumulation of beta-catenin in Hela cells, which thus provides a mechanism for the function of Grp58 in Hela cell migration. Finally, the authors showed an inverse expression of Grp58 and beta-catenin in human cervical cancer.

Although the authors provide some clues that suggest a link between Grp58, beta-catenin, and cervical cancer, in its form this manuscript does not provide sufficient and convincing data to demonstrate this link. The authors may wish to address the following.

Major concerns:
1. Figure 1A has been presented in their previous publication (please refer to Figure 3A in Liao et al, Cancer Sci, 2011:2255-63).
2. All in vitro data were done in Hela cells. At least an additional cell line is required to verify/strengthen the link between Grp58 and beta-catenin.
3. Similarly, because all in vitro experiments were performed in one cervical cancer cell line, the title and conclusions appear overstated.
4. There is no “statistical analysis” in the Methods.

Minor concerns:
1. Table 1: The Affymetrix microarray showed that some genes involved in Wnt signaling displayed altered expression in Grp58 knockdown cells. The authors should perform qRT-PCR and/or western blot to verify these alternations.
2. Figure 1: Please provide what is “L” and “G” stand for in the figure legends?
3. Figure 1: The basal level of beta-catenin in Fig 1A & 1C were barely detectable. Moreover, as shown in Fig 1A & 1C, the basal level of beta-catenin in Grp58 knockdown cells were markedly higher than that in control cells. However, as shown in Fig 1D, the basal beta-catenin protein in control cells appears higher and the difference of basal beta-catenin protein between control and Grp58 knockdown cells were modest. Any explanation?
4. Figure 1B: Statistical analysis?
5. Figure 1D: Please insert the information of CHX treatment in the presentation for easier understanding.
6. Figure 4B: Why there are some free dots?
7. Please provide some information concerning beta-catenin and Wnt signaling in the Introduction.
8. Please provide some explanation why beta-catenin was chosen for investigation, since it was not included in the gene list identified by microarray analysis. (In the result part “Grp58 regulates beta-catenin protein stability”)
9. “As shown in Figure 1A and B” should be changed to “As shown in Figure 1A”, because Fig 1B shows the mRNA levels of beta-catenin, but not its protein levels. (In the result part “Grp58 regulates beta-catenin protein stability”)

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.