Reviewer's report

**Title:** Temporal Evolution in Caveolin 1 Methylation Levels During human Esophageal Carcinogenesis

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**Reviewer:** Sung-Gil Chi

**Reviewer's report:**

In this manuscript entitled "Temporal Evolution in Caveolin 1 Methylation Levels During human Esophageal Carcinogenesis" the authors investigated whether and at which neoplastic stage promoter hypermethylation of CAV1 is involved in human esophageal carcinogenesis. The authors found CAV1 methylation is significantly higher in Barrett’s metaplasia (BE), low-grade and high-grade dysplasia occurring in BE, esophageal adenocarcinomas (EAC), esophageal squamous cell carcinomas (ESCC) than in normal esophagus. They also observed that normalized methylation values (NMVs) of CAV1 in EAC and ESCC are significantly higher than in corresponding NE. Based on these findings, they concluded that CAV1 promoter hypermethylation is a frequent event in human esophageal carcinomas and is associated with early neoplastic progression in Barrett’s esophagus.

In overall, the manuscript is well organized and contains potentially interesting findings. However, there are some concerns.

1. Although this study contains well-performed statistical and comparative analysis of CAV1 methylation, the manuscript lacks the novelty considering that several previous studies reported CAV1 methylation status in subtypes of esophageal cancer.

2. The CAV1 promoter includes several CpG-rich regions which display differential methylation patterns depending on types or stage of tumors. In this context, authors need to provide more detailed information and analysis results for the promoter region (CpG sites) examined in this study.

3. Considering the possible differential effects of the CpG-rich regions on gene transcription as mentioned above, authors need to validate that the promoter methylation status reflects CAV1 protein expression status in tumor tissues.

4. Authors found no significant association between CAV1 promoter hypermethylation and pathological characteristics of tumors and patient survival. In this context, authors need to describe clinical relevance of their findings.

5. Several previous studies demonstrated that expression of CAV1 and/or CAV1 is elevated in esophageal squamous cell carcinoma compared to corresponding normal tissues and its elevation is associated with malignant progression and poor survival of the patients (Cancer 2002: 94:929-33; Oncol Rep. 2007)
Therefore, authors need to discuss in more detail on this discrepancy.

**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