Reviewer’s report

Title: Analysis of cell cycle-related proteins in gastric intramucosal differentiated-type cancers based on mucin phenotypes: a new concept of molecular carcinogenesis for early differentiated-type gastric cancers

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Reviewer: Yusuke Tajima

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The authors examined the relations between abnormalities of cell cycle-related proteins and mucin phenotype in the early phase of differentiated-type gastric cancers. From the findings of the study, the authors concluded that the cellular mucin phenotypes of intramucosal differentiated-type adenocarcinomas of the stomach are dependent on distinct cell cycle-related alterations, and that the clinicopathological findings result from different pathways based on mucin expression. The authors analyzed the large amount of data using a lot of immunohistochemical markers. Although this is an informative paper, there are several shortcomings that should be revised.

Major comments

(1) Gastric phenotype cancers may include several types of cancers, such as MUC5AC+ and MUC6+, MUC5AC+ and MUC6-, and MUC5AC- and MUC6+. Intestinal phenotype cancers also include MUC2+ and CD10+, MUC2+ and CD10-, and MUC2- and CD10+. In fact, the authors noted that intestinal phenotype tumors were sub-classified into 2 groups: colonic type (positive for MUC 2 only) and small intestinal type (positive for CD10) (page 7, line 7). The authors should mention the differences in clinicopathological features and immunohistochemical factors examined among these subgroups.

(2) Some findings on the relations between mucin phenotype and expressions of the cell cycle-related proteins determined in this study seem to overlap with those in the previous papers. As a result, it is difficult to understand the new findings by this paper analyzing the large amount of data. The authors need to further distinguish their results from previous studies by others, perhaps in a summary matrix table that would simplify understanding by the reader.

Minor comments

(1) The authors used the word “mucin phenotype”. However, does CD10 immunoreaction mean “mucin” expression?

(2) This study showed that p53 expression was more frequently found in gastric phenotype cancers. However, previous papers reported that p53 mutation was rather the characteristic of intestinal phenotype cancers or cancers with CD10 expression (Endoh et al. J Pathol 2000;191:257-263, Tajima et al. Clin Cancer Res 2006; 12: 6469-6479). It is necessary to discuss with these papers.
(3) Figures
The figures showing expressions of mucin markers are needed?

(4) Table 3, figure 2, and figure 4
Gastric (intestinal, mixed, or unclassified) “type”?
Is gastric (intestinal, mixed, or unclassified) “phenotype” correct?

**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