Reviewer's report

Title: The overmethylated genes in Helicobacter pylori-infected gastric mucosa are demethylated in gastric cancers

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Reviewer: Hiromu Suzuki

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In this manuscript, Hong et al. demonstrated that methylation of transitional CpG sites are influenced by (1) distance from retroelements, (2) lack or presence of CpG island, (3) H. pylori infection in non-cancerous gastric mucosa and (4) LOH status in cancer. These findings are quite interesting and important, although the first and second points are already described in their previous reports. However, there are several concerns as listed below, which requires revision of this manuscript before acceptance.

Major Compulsory Revisions

1. Does methylation in the transitional CpG sites correlate with gene expression in the specimens used in this study? Only the SAGE tag results in normal stomach is shown, and this point is not mentioned.

2. Is there any correlation between the transitional CpG sites methylation and neighboring CpG island methylation? It is of interest to see whether CpG islands are methylated or not, when the neighboring transitional CpG sites are methylated by H. pylori infection.

3. Page 18: Are there any functional evidence for the statement "In cancer tissue that undergoes the LOH event that reduces a gene dose, the remaining gene copies have the increased possibility of using the nuclear proteins and this would lead to the demethylation of transitional-CpG segments"? If so, please include a citation for this statement. If not, please show functional evidence that hypomethylation is a consequence of LOH in cancer.

4. Page 21: "This study suggests that the concurrent methylation of multiple CpGisland genes initiates and sustains the adaptive differentiation of newly fixed stem cells in the gastric mucosa infected with H. pylori, and that the LOH-induced DNA demethylation and discordant methylation of stomach-specific genes may facilitate gastric carcinogenesis by reactivating a stem-cell intrinsic program." This study does not provide enough functional evidences to draw this conclusion.

Minor Essential Revisions

5. "Overmethylation" and "Undermethylation" are not commonly used terms to describe DNA methylation, and the authors have used "hypermethylation" and "hypomethylation" in their previous manuscript (Kim YH et al. BMC Cancer, 2006). Is there any specific reason to use these uncommon terms in this
manuscript?

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.