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May 12th, 2013

RE:
Title: DNA Methylation in Inflammatory Bowel Disease and Beyond
Authors: Daren Low, Atsushi Mizoguchi, Emiko Mizoguchi
Name of Journal: *World Journal of Gastroenterology*
ESPS Manuscript NO: 3063

Dear Editor,

Thank you very much for informing us that this review article will be accepted after minor revisions by the journal. I have read the reviewers' comments with interest, and I'm very glad that the reviewers highly recommended this manuscript for publication. I have revised the manuscript according to editors' suggestions, and all changes are yellow-marked. The format of the manuscript has been updated in accordance to editorial suggestions. This includes the addition of a running title, core tips, authors contributions and key words. In addition, the annotations for references within text have also been corrected.

We hope that the revised manuscript is satisfactory; having addressed the issues raised by the editors and reviewers, and is now suitable for the publication in WJG. If you have any questions, please feel free to contact me.

Sincerely yours,

Emiko Mizoguchi, M.D., Ph.D.
Assistant Professor of Medicine
Harvard Medical School

EM/tdl

Point-by-point response to reviewers' comments

1. **Reviewer 1 (00041468):**
"It is a very interesting review about a hot topic of IBD. The style is well written, easy to read, the discussed aspect are also logical and comprehensive. It is known, that the changes of the CpG pattern have pathologic effect in the develoment of mucosal inflammation. Whether (self-)DNA (CpG DNA from host) itself has any biologic effect on IBD? How does self-DNA methylation relate to TLRs (namely TLR9)? Has this effect any clinical significance? The discussion of this aspect of DNA metylation in IBD therapy would enhance the strenght of this review. The form of the manuscript must be changed to the requirements of WJG After major revision, I suggest to accept the manuscript for publication in WJG."

Our response: As commented by the reviewer, the relevance of self-DNA in IBD development is indeed very interesting. Particularly, unmethylated DNA derived from bacterial, as well as methylated DNA derived from host cells, can induced inflammatory responses through TLR9 that may has consequences in IBD development. A discussion on this aspect has been included in the revised manuscript. The format of the manuscript has also been modified according to editorial suggestions.

2. **Reviewer 2 (00608190):**
"This review focuses on the impact of epigenetics on the pathogenesis of inflammatory bowel disease (IBD) and IBD-associated colorectal cancer. The insight in this review may help more understanding of these diseases, whereas an accurate comprehension of them requires knowledge for diverse research areas. To easily understand the context of the review including "omics", oncology, microbiology, and immunology, the author should show the characteristics of each disease described in the manuscript, using figures and/or tables. The author should correct some English writing errors. Additionally, EZH2 means Enhancer of Zeste Homolog 2."

Our response: We have now included an additional table (Table 1) and figure (Figure 2) to give an overview of the methylomics advancements and the impact of microbiology in DNA methylation in IBD, respectively. This is in addition to the existing figures that show the potential roles and expression of DNMTs in the different IBD diseases (Figure 1), as well as the temporal events that has an impact in DNA methylation changes in IBD (Figure 2). The full term of EZH2 has also been corrected to "Enhancer of Zeste Homolog 2".

3. Reviewer 3: 00055041: "TITLE: DNA Methylation in Inflammatory Bowel Disease and Beyond Comment This is an interesting paper. The results are clear and well described. In the Discussion, the Authors should highlight the possible clinical significance of their findings."

Our response: We have now included additional clinical significance discussion in appropriate sections of the revised manuscript.