Reviewer’s report

Title: The role of prostaglandin E2 (PGE2) in toll-like receptor 4 (TLR4)-mediated colitis-associated neoplasia

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Reviewer: Shin Maeda

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Major Compulsory Revisions

This manuscript investigated the effect of PGE2 on colitis-associated neoplasia. The result may be potentially interesting, but there is a question about experimental design and there are some key data missing from this work.

1. The authors described that no significant difference was seen in the incidence of colitis-associated neoplasia between the mice treated with PGE2 during DSS treatment and treated with PBS, and that increased mucosal PGE2 during the acute phase of colitis does not promote tumorigenesis. However, the number of the mice treated with PGE2 was 5, and only one mouse developed dysplasia. The number of mice treated with PBS was 6, and only two mice had dysplasia. These numbers seemed to be insufficient to assess. Previously the authors showed PGE2 ameliorates acute colitis in TLR4-/- mice if administered during DSS treatment in Ref.27. Why didn’t the decreased inflammation in PGE2-treated mice reduced the development CAC in this study?

2. The authors described that the mice in the acute phase of colitis had significantly higher production of mucosal PGE2 than the mice in the chronic phase (331.0 vs. 223.8). I think that the amount of PGE2 which was administered during DSS treatment was insufficient because mucosal PGE2 increased during DSS treatment, and that relatively low dose of PGE2 may decrease the phenotypic difference. Does treatment with more doses of PGE2 during DSS influence the colitis activity or the development of CAC?

3. The authors showed that PGE2 plays different roles during the acute and the chronic phases of colitis. The authors should examine whether the administration of PGE2 during or after DSS treatment affects the colitis activity by BW change, disease activity score, or histological score, and compare both administration protocols.

4. The authors showed the total histological score of AOM-DSS-treated mice in Figure 3A, but the authors should show details of this score, for example, the infiltration of myeloid cells and the epithelial cell damage. “NS” was described in this figure, but the difference between WT and PBS-treated TLR4-/- mice seems to be significant.

5. In Figure 3, B and C, the authors showed mucosal 15d-PGJ2 synthesis was up-regulated in day7, but not in recovery phase. However, the authors described
“Exogenously administered PGE2 disturbs the balance between cell-proliferative and anti-inflammatory prostanoids during the recovery phase but not during the acute phase of colitis.” This is a little confusing. When does mucosal 15d-PGJ2 play an important role, during the acute phase or in the recovery phase?

6. In Figure 3, B and C, the authors should show the time course of mucosal 15d-PGJ2 synthesis in WT mice and TLR4-/− mice.

7. In Figure 4, were these colonic sections removed from AOM-DSS-treated mice? If so, the authors also should perform BrDU assay without AOM-DSS.

8. In Figure 5, the authors should analyze the expression of AR and p-EGFR in non-tumor epithelia and tumor section separately.

9. In Figure 6A, the expression of Cox-2 was elevated in the mice treated with high-dose PGE2. Were other inflammatory cytokines, such as TNF, IL-6, or MIP2, also elevated?

10. In Figure 6C, the authors should include the data using TLR4-/− macrophages.

11. In Ref.27, it was said that there was a significant decrease of apoptotic cells in PGE2-treated TLR4-/− mice compared with vehicle-treated TLR4-/− mice. The authors should include the analysis of apoptosis in this study because it has been shown that apoptosis plays an important role in the development of CAC.

Level of interest: An article whose findings are important to those with closely related research interests

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

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.