

## Peer Review File

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### Reviewer A

**Comment 1:** Unfortunately, it was difficult to find novelty in this paper that differed from previous reports. There have been already many reports related to cancer proliferation and anti-apoptosis by DHODH in colorectal cancer and esophageal squamous cell carcinoma. Leflunomide used as a DHODH inhibitor is also well-known.

**Reply 1:** We carefully revised and improved our manuscript.

### Reviewer B

In the manuscript, the authors showed role of gene DHODH, an enzyme for pyrimidine synthesis pathway, for cancer cell prognostics especially in esophageal cancer and colon cancer. By pan-cancer analyses, the authors compared the expression of DHODH in cancer tissues and normal tissues and on patient survival. Then, they specified the DHODH in ESCC and CRC further.

It is interesting to show the importance of the gene DHODH in ESCC and CRC, however, the manuscript should be improved before publication.

**Comment 1:** Through Figure 1-3, the authors should point out what they would like to focus on. Some figures might go as supplementary figure and others related to ESCC and CRC remain as main figure. Especially, I don't understand why figure 2 and figure 3 are not combined. They are not about CRC either ESCC.

**Reply 1:** According to the reviewer's suggestion, we carefully revised our manuscript. We changed Figure 1B and 1C (old version) to Figure S1A and S1B (new version). We combined and changed Figure 2 and Figure 3 (old version) to Figure S2 (new version). Figures 4-8 (old version) were changed to Figures 2-6 (new version).

**Changes in the text:** We changed Figure 1B and 1C (old version) to Figure S1A and S1B (new version). We combined and changed Figure 2 and Figure 3 (old version) to Figure S2 (new version). Figures 4-8 (old version) were changed to Figures 2-6 (new version). We also revised all the corresponding description in the main text, figure legends and supplement figure legends.

**Comment 2:** It would be more helpful to show correlation between SLC7A11, GPX4 DHODH in some dataset from cancers in figure 4.

**Reply 2:** According to the reviewer's suggestion, we analyzed the correlations between SLC7A11, GPX4 and DHODH in the datasets of GSE53622 and GSE53624 (Figure 4 old version). The results showed that expression of DHODH was positively correlated with SLC7A11 mRNA level both in GSE53622 and GSE53624 datasets, and correlation

between expressions of DHODH and GPX4 were only identified in GSE53624 dataset, and there was no correlation between expressions of SLC7A11 and GPX4 in two datasets (Figure 2G-2L, new version).

**Changes in the text:** We analyzed the correlations between SLC7A11, GPX4 and DHODH in the datasets of GSE53622 and GSE53624 (Figure 4 old version) and showed the results in Figure 2G-2L and on page 17 line 191-194. We also added the corresponding figure legends.

**Comment 3:** It would be helpful to provide mutation profile of cancer cell lines if it is available in figure 5, 6.

**Reply 3:** We appreciate the reviewer's suggestion, but we are sorry that we didn't detect the mutation profile of cancer cell lines which are used in our study.

**Changes in the text:** Not applicable.