Dear reviewers,

We are so appreciate for your letter about our paper. Overall the comments and advice are helpful. We have learned much from it. After carefully studying the reviewer's comments, we submit here the revised manuscript as well as a list of changes.

If you have any question about this paper, please don't hesitate to let us know.

Response to reviewers:

Reviewer #1：

This is an acceptable paper, which makes a solid contribution to the field. However, some minor revisions are required.

1. First, with respect to the RNA isolation and subsequent quantitative real time RT-PCR, were any controls performed to test for genomic DNA contamination? For example, were any samples processed without the RT step, which should yield no PCR product in the absence of DNA contamination?

Response: Thanks for reviewer's advice. In our study, the positive control (genomic DNA) and negative controls (PBS and samples processed without the RT step) were performed in quantitative real time RT-PCR. We have also described this in the Materials and Methods section.

2. The methods section also needs a description of the WNT luciferase reporter assay from Figure 5B. What reporter was used? Was a mutant control also evaluated to ascertain whether effects are specific to Wnt activity? For example, if TOPFlash was used as the WNT reporter, then that activity needs to be normalized to the FOPFlash control. While I understand that Wnt target genes exhibited altered expression as shown in Fig. 5C, one could argue that that the effects are not necessarily specific to WNT signaling.

Therefore, using the mutant control promoter in Fig. 5B would strengthen the conclusions for both 5B and 5C.

Response: Thanks for reviewer's advice. In our study, the TOP/FOP Flash WNT luciferase reporter assay was used. It is sorry for that we forgot to describe the method. We have also described this in the Materials and Methods section.

3. In the Discussion, the sentence that begins "Colorectal tumorigenesis is activated…" suggests that colorectal cancer is initiated by WNT ligand-Frizzled receptor binding (which is actually what normal WNT signaling is). In actuality, most colorectal cancer is initiated by mutations in the WNT signaling pathway (e.g., APC or beta-catenin) that constitituvely activate the pathway even in the absnce of ligand-receptor buindinf. Of course, such neoplastic cells can also have additional WNT signaling through ligand-receptor activity, and that can promote progression, however, the main activity of WNT signaling in colorectal cancer is typically the result of mutations that drive WNT signaling even in the absence of ligand-receptor binding. That should be modified as well.

Response: Thanks for reviewer's advice. We are sorry for the mistake. We have made appropriate correction in the revised manuscript.

4. A minor issue: there are some grammar errors, please edit. For example, should be "ESCC cell proliferation" not "ESCC cells proliferation. Also, should be either "activating the WNT signaling pathway" or "activating WNT signaling" not "activating WNT signaling pathway.

Response: We apologize for these errors. We have corrected these errors in the revised manuscript.

Reviewer #2：

In this study, authors identified the potential role of miR-30a-3p/5p in esophageal squamous cell carcinoma progression. This is a well-defined study and the MS is written and organized well. Authors showed that down-regulating miR-30a-3p/5p promotes ESCC cells proliferation by activating WNT signaling pathway. However, the connection between miR-30a-3p/5p and WNT signaling is weekly shown in the MS.

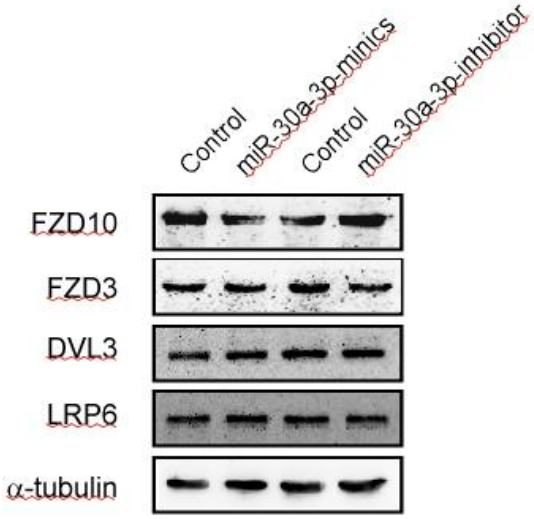
Concerns:

1. KEGG pathway enrichment analyses of miR-30a-3p and miR-30a-5p target genes (figure. 5) shows that multiple pathways are enriched (Ras, MAPK, FoXo, Hippo and WNT). How authors selected WNT signaling among the other signaling events? Ras, MAPK are highly enriched. Authors should explain this.

Response: Thanks for reviewer's advice. It is well known that microRNAs serve as a post-transcriptional regulator by directly many targeting mRNAs in many kinds of biological processes. Our team focuses on the function of the WNT signaling pathway in the progression of ESCC, so we mainly explore this signaling pathway. We also appreciate the reviewer's points and take them into good consideration in our next study.

2. In figure 6 C. did authors check the inhibitory effects of miR-30a-3p and miR-30a-5p on different Wnt ligands?

Response: Thanks for reviewer's advice. We also checked the inhibitory effects of miR-30a-3p and miR-30a-5p on different Wnt ligands, but there is no significant difference between control group and treated group, as is showed in the following figure.


Control
miR-30a-3p-mimics
Control
miR-30a-3p-inhibitor
FZD10
FZD3
DVL3
LRP6
α-tubulin