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## Reviewer A

**Here are the general comments from the reviewer.**

Tu et al. reviewed lncRNAs in PCOS in this manuscript. They first organized the general knowledge of lncRNAs and then described concrete examples of lncRNAs in PCOS. However, they just describe or enumerate the findings of each work, and what they want to claim from those findings are not clearly stated.

Response: Thanks very much for taking your time to review our manuscript. We really appreciate all your comments and suggestions. There is no review to summarize the relevant studies. The highlight of our review is that we summarize in detail aberrant lncRNAs in different specimens of women with PCOS (i.e., granulosa cells, cumulus cells, peripheral blood) and PCOS rodent models. We aim to discuss the mechanism of dysregulated lncRNAs in PCOS and classify various lncRNAs accordingly. We found that lncRNAs played a molecular role in PCOS mainly by functioning as ceRNAs. However, there is insufficient evidence to generalize other molecular mechanisms. We can recognize the limitations of these studies, and provide potential ideas for the future research and the transformation of clinical diagnosis and therapies. We re-read these literature and added relevant references to state what we want to claim (e.g. see Page 11-12, line 228-231;Page 17-19, line 357-379;).

In addition, their description is not accurate in some parts, and references are insufficient.

Response: Thank you for underlining this deficiency. We are sorry that we did not correctly describe the relevant definitions and did not adequately search the literature. We have revised the incorrect description (e.g. see Page 7, line 135-137; see Page 8, line 147-149) and cited some references (see Page 9, line 168-173) according to your comment.

For publication, they need to re-organize the entire manuscript, such that the findings in reference papers are better organized and they describe much more about what they can say from those findings.

Response: Thank you for your suggestion. To better illustrate our views, we have re-organized the manuscript. We added a separate section to describe what is known on lncRNAs in normal reproductive physiology (see Page 9-10, line 165-197) and revised our views in the conclusion (see Page 17-19, line 354-379).

Also, English language should be edited, all their description needs to be accurate, and citation should be sufficient.

Response: Thank you for your suggestion. We have modified the incorrect description (e.g. see Page 7, line 135-137) and cited some references to enrich the content (see

Page 9, line 168-173). Our manuscript has been edited by professor John R.G. Challis who is a native English-speaking expert in the Departments of Obstetrics and Gynaecology at the University of Toronto; and our colleague Siwen Wang, a visiting student in Harvard Medical School, also helped to edit the text.

The followings are some examples to be improved. Note that these are just examples and the authors need to revise more for publication.

**Specific comments**:

**Line 96**; They should cite original papers of the description. In this case, instead of reference 6, they should cite [Science 309:1559, 2005] and [Science 309:1564, 2005].

Response: Thank you for your suggestion. We have removed reference 6 and cited [Science 309:1559, 2005] and [Science 309:1564, 2005] according to the comment. Additionally, we cited [Nature 447:799-816, 2007] to fully illustrate the description (see Page 5, line 85-88).

**Line 144-146;** The authors' description of cis- and trans-regulation is not accurate. Even if the target is located in a distant locus, it is called "cis-regulation" when the target is on the same chromosome. Only when the target is present in a different chromosome from the lncRNA, the mechanism is called "trans-regulation".

Response: Thank you for your comment.We have modified this expression according to the comment and reference .This sentence was rephrased as follows "LncRNAs can act on their target genes through cis-regulation, affecting expression of the neighbouring gene on the same allele from which they are transcribed. In trans-regulation, lncRNAs do not meet this criterion. " (see Page 7, line 134-137).

**Line 156-159**; Chromatin-remodeling factors and histone acetylases are not transcription factors. They affect the binding of transcription factors by modifying chromatin.

Response: Thank you for the comment. This incorrect description were revised as follows "Some lncRNAs interface with additional regulators (i.e., ATP-dependent chromatin remodeling complexes and histone acetyltransferases) to affect gene expression. " according to the comment (see Page 8, line 147-149).

**Line 184**; This reviewer does not know the policy of this journal, but "granular cell" is not usually used. "Granulosa cell" should be used.

Response: Thank you for your suggestion. We have replaced "granular cell" by "granulosa cell" throughout the text according to the comment (e.g. see Page 11, line 208)

**Line 198-200**; The in vivo function of Neat1 was evaluated by the KO mouse model, so they should cite [Development 141:4618, 2014].

Response: Thank you for the suggestion. We have cited [Development 141:4618,

2014] according to the comment (see Page 9, line 170-173).

**Reviewer B**

**Here are the general comments from the reviewer.**

The manuscript by Tu et al reviews the role of lncRNAs in PCOS. Given the emerging roles of lncRNAs in various human diseases, the subject of this review is timely and relevant. However, the manuscript in its current form needs enhancements.

Response: Thanks very much for taking your time to review our manuscript. We really appreciate all your comments and suggestions. Here are our itemized responses in below.

**Specific comments**:

1) Though the manuscript is legible, English language style and accuracy must be significantly improved. Early in the abstract, there are misused words. Just to mention, I suggest replacing "abundant" for "many"; "understood" by "studied".

Response: Thank you for your pertinent comment. We have re-edited the English language with the help of professor John R.G. Challis who is a native English-speaking expert in the Departments of Obstetrics and Gynaecology at the University of Toronto; and our colleague Siwen Wang who is a visiting student in Harvard Medical School. We have modified the misused words throughout the text and replaced "abundant" for "many"; "understood" by "studied" according to the comment (see Page 3, line 42-44).

2) Lines 113-114 are not clear in what they mean saying "ncRNAs are short of translated open reading frames…". In line 120 replace "distinguished" by "distinctive". Language style must be improved

Response: Thank you for your comment.

**Lines 113-114**; We were sorry for the vague description.We modified the sentence to "By comparison to mRNA, lncRNAs lack open reading frames (ORFs) but have special 3-terminal processing and a greater tendency towards cell type-specific expression." (see Page 6, line 103-105)

**Line 120**; we have replaced "distinguished" by "distinctive" as advised (see Page 6, line 110) and improved the language style with the help of professor John R.G. Challis (University of Toronto) and our colleague Siwen Wang (Harvard Medical School) .

3)There is not an actual difference of contents between sections 3.1 and 3.2

Response: Thank you for the comment.We agree with you. In section 3.1, more description are the biogenesis and structure of lncRNA. In section 3.2, the function of lncRNA is mainly discussed. We kept the subtitle to highlight the main idea, but removed the number (see Page 5-6, line 85-120).

4) Should “hit theme” would be “hot theme”? (line 142). Line 179, “scientists discover” is not an appropriate word. Line 184 and ahead, replace “granular cells” by “granulosa cells”. Line 266 replace “peripherial” by “peripheral”. Line 533, revise the meaning of sentence “Most lncRNA are not clear about the function”.

Response: Thank you for the suggestion.

**Line 142**; we have revised the sentence “LncRNAs function in the epigenetic regulation has been a hit theme. “ as follows “The role of lncRNAs in the epigenetic regulation has been of considerable interest. ” (see Page 7, line 132).

**Line 179**;we have revised the sentence “scientists discover numerous lncRNAs are involved in various biological” as follows “many studies have described numerous lncRNAs in various biological and pathological processes” (see Page 10, line 203).

**Line 184**;we have replaced “granular cells” by “granulosa cells” as advised (see Page 11, line 208).

**Line 266**; we have replaced “peripherial” by “peripheral” as advised (see Page 14, line 288).

**Line 533**; we have revised the sentence “Most lncRNA are not clear about the function”as follows “The function of most listed lncRNAs has not been investigated.” (see Page 30, line 599-600).

5) Prior to section 4, a brief paragraph describing what is known on lncRNAs in ovarian development and reproductive cycle should be added. For example, the paper by Nakagawa et al (Development. 2014 Dec;141(23):4618-27) should be added. Segments in section 4.2 could be relocated to satisfy this request.

Response: Thank you for the suggestion.We have added a separate section to describe what is known on lncRNAs in normal physiology (see Page 9, line 165). We relocated segments in section 4.2 into the new paragraph as you advised (see Page 9, line 183-185). Also, we cited [Development 141:4618, 2014] and added other relevant references to enrich the content (see Page 9, line 167-173).

To be useful as a review, this manuscript should describe clearly a contrast between the regulatory roles of lncRNAs in normal physiology and in pathology.

Response: Thank you for the suggestion.There is insufficient evidence to demonstrate the roles of lncRNAs in the physiological function of ovary. It is inadequate to make a detailed comparison bewteen the regulatory roles of lncRNAs in normal physiology and in pathology. We briefly describe the difference between the lncRNAs in normal physiology and in PCOS during the follicle development according to your suggestion (see Page 18, line 359-360).

6) Line 190 refers to Fig1 as a “network”. There is actually no network in it, just gene lists. Please correct the text.

Response: Thank you for the comment. We have revised the sentence as follows “ LncRNAs has been involved in diverse manifestations of PCOS mainly through the

interaction between lncRNA and miRNA." (see Page 11, line 213-214).