

Reviewer 1 | 12 Jun 2021 | 19:59 #1

The manuscript is well written. I have only minor suggestions.

1. Reference #33 is not appropriate. This reference is not cumulus-oocytes. There are MANY good references on cumulus-oocyte communication regarding cGMP/cAMP. Also, in the manuscript at line 156, cGMP is the primary molecule that transfers from cumulus cells to the oocyte. The cGMP cascade controls the cAMP in the oocyte. See articles by Dr Laurinda Jaffe's research group.
2. A figure or table showing the 8 potential markers and how they affect the oocyte would be an interesting, but not essential addition.
3. Please add information on how these markers are being detected in the studies referenced. Are they running standard RT-qPCR on granulosa cells, cumulus cells, or culture media?

QUALITY ASSESSMENT

Q 6	Quality of generalization and summary	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Q 7	Significance to the field	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>



Q 5 Please provide your detailed review report to the editor and authors (including any comments on the Q4 Check List):

Reviewer 2 | 21 Jun 2021 | 02:42 #1

The authors should provide a table to show other biomarkers associated with oocyte maturation which were not discussed in the MS and give a short description about their function and disadvantages for not be good biomarkers. Correspondingly, some words should be added in discussion.

My main suggestion is to include a diagram to show the distribution of these non-invasive biomarkers during the process of egg cell maturation in cumulus-oocyte complex. In this way, it is easier for non professional readers to understand.

Other suggestion, the different genes encoding secreted peptides between mature and immature oocytes could be revealed by deep-sequencing and these peptides could be as candidate biomarkers. Could the authors collected the data (if any) and discuss the point?

Corresponding Author: Batara Sirait | 19 Jul 2021 | 15:09 #2

We appreciate the time and effort that you have dedicated to providing your valuable feedback on our manuscript. We are also grateful to receive your insightful comments. Here are our responses for your comment and suggestion:

1. A paragraph has been added to discuss other biomarkers that were expressed differently in oocytes of different

Oocyte Competence Biomarkers Associated with Oocyte Maturation: A Review

BataraSirait* , Budi AuliaWiweko, [Budi Wiweko](#), [Dein Iftitah](#) and Raden Muharam

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Research Topic: [Germ Cell Development and Reproductive Aging](#)

Keywords: oocyte competence, Oocyte maturation, Cumulus-oocyte complex (COC), biomarker, in-vitro fertilization

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You are pending to respond to Reviewer 2 and/or resubmit a new version of your manuscript.

Reviewer 1 endorsed publication of this manuscript.

	Reviewer 1	Author comments for reviewer 1	Reviewer 2	Author comments for reviewer 2
Recommendation for the editor	The manuscript can be accepted		Revision is required	
Please provide your detailed review report to the editor and authors	<p>The manuscript is well written. I have only minor suggestions.</p> <p>1. Reference #33 is not appropriate. This reference is not cumulus-oocytes. There are MANY good references on cumulus-oocyte communication regarding cGMP/cAMP. Also, in the manuscript at line 156, cGMP is the primary molecule that transfers from cumulus cells to the oocyte. The cGMP cascade controls the cAMP in the oocyte. See articles by Dr Laurinda Jaffe's research group.</p>	<p>1. Reference #33 has been updated with a relevant one. cGMP has been added as one of the factors causing Meiotic maturation arrest.</p> <p>2. A figure has been added to better visualize the potential role of each gene in predicting an IVF outcome</p> <p>3. Detection of each of these markers is described in the summary table 1. In most of the referred studies, extraction of genetic material from the cumulus and</p>	<p>The authors should provide a table to show other biomarkers associated with oocyte maturation which were not discussed in the MS and give a short description about their function and disadvantages for not be good biomarkers. Correspondingly, some words should be added in discussion.</p> <p>My main suggestion is to include a diagram to show the distribution of these non-invasive biomarkers during</p>	<p>We appreciate the time and effort that you have dedicated to providing your valuable feedback on our manuscript. We are also grateful to receive your insightful comments. Here are our responses for your comment and suggestion:</p> <p>1.A paragraph has been added to discuss other biomarkers that were expressed differently in</p>

	<p>2. A figure or table showing the 8 potential markers and how they affect the oocyte would be an interesting, but not essential addition.</p> <p>3. Please add information on how these markers are being detected in the studies referenced. Are they running standard RT-qPCR on granulosa cells, cumulus cells, or culture media?</p>	<p>granulosa cells was conducted followed by quantification of the gene of interest through PCR methodology.</p> <p>#Kindly notice that we have addressed minor suggestions from reviewer 1 as follow:</p> <ol style="list-style-type: none"> 1. Reference #33 has been updated with a relevant one. cGMP has been added as one of the factors causing Meiotic maturation arrest. 2. A figure has been added to better visualize the potential role of each gene in predicting an IVF outcome 3. Detection of each of these markers is described in the summary table 1. In most of the referred studies, extraction of genetic material from the cumulus and granulosa cells was conducted followed by quantification of the gene of interest through PCR methodology. 	<p>the process of egg cell maturation in cumulus-oocyte complex. In this way, it is easier for non professional readers to understand.</p> <p>Other suggestion, the different genes encoding secreted peptides between mature and immature oocytes could be revealed by deep-sequencing and these peptides could be as candidate biomarkers. Could the authors collected the data (if any) and discuss the point?</p>	<p>oocytes of different maturity but have not been proven to hold a significance value in predicting IVF outcomes.</p> <ol style="list-style-type: none"> 2. Instead of creating a diagram for the oocyte maturation process, to define the focus in this study, we added a figure to better demonstrate which of the IVF outcome events that the each of the COC biomarkers discussed here could potentially predict. 3. A study by Wyse et al., 2020 which utilized NGS to obtain genes that are differentially expressed between mature and immature oocytes has been included in this study. Further research however is required to assess these candidate biomarkers by tracking the outcome of each gene expression in individual oocyte, as described in the discussion.
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EDITOR

Handling Editor: Francesca Elizabeth Duncan

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Interactive review activated date: 02 Jul 2021

You can post new comments and reply to the handling editor's comments here. On completion, ensure you click on **Submit all comments** to alert the handling editor of your entries. Note that the reviewers can also read these comments.

<p>Reply for the editor</p> <p>Dear Francesca Elizabeth Duncan Editor of Front. Cell Dev. Biol. - Molecular and Cellular Reproduction</p> <p>We thank you immensely for giving us the chance to revising our manuscript. Our reply point-to-point according to reviewer comments or suggestion has been explained within the revised version. All changes have been highlighted using the track-changes mode.</p> <p>Thank you</p>	
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