Reviewer's report

Title: Regulation of Gene Expression in Ovarian Cancer Cells by Luteinizing Hormone Receptor Expression and Activation

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Reviewer: Katja Teerds

Reviewer's report:

Cui and colleagues describe a cell model to determine the impact of LH receptor expression and LH-mediated LHR activation on gene expression in the ovarian surface epithelial cell line SKOV-3. They perform a microarray analysis performed and report differential expression of nearly 1800 genes in LH-treated cells. The authors conclude that their study shows extensive transcriptomic changes of ovarian cancer cells in response to LH receptor activation, which provide a comprehensive and objective assessment for determining new cancer therapies and potential serum markers.

In general the manuscript is well written and the data presented interesting, though descriptive. Especially the lack of further quantitative analysis of relevant genes from the gene families identified by the authors is a serious draw back of the manuscript in its present form.

Comments:

1. A more quantitative approach would improve the quality of the manuscript. On the other hand, the same group has already described some quantitative changes in gene expression under the influence of LH receptor activation in SKOV-3 for genes involved in cell adhesion and metalloproteinases (see ref. 14). Concerning these gene families, the present manuscript is confirmatory and one would have expected the authors first to perform the microarray analysis and then continue, as suggested above, with quantification of specific, important genes with a qRT-PCR analysis.

(Major compulsory revision)

2. How representative are SKOV-3 cells for normal ovarian surface epithelial cells and OSE derived ovarian cancer cells, as these cells all express LH receptors. The study would improve if the authors include another OSE cell line. In figure 5 the authors show a heatmap for differentially expressed genes between SKOV-3 cells and HOSE cells. The experiment with the HOSE cells is not described in the manuscript nor is indicated which gene families show differential expression? Are there similarities with the SKOV-3 cells? The study seems at present incomplete.

(Major compulsory revision)

3. The conclusions drawn by the authors are speculative and not supported by the data shown in the present study. Without expanding the gene analysis data
to the protein level, one can not conclude that >100 proteins may be secreted into the circulation in response to LH receptor activation in SKOV-3 cells and that the present study therefore provides a comprehensive and objective assessment for determining new cancer therapies and potential serum markers.

Major compulsory revision)

4. Introduction

P.3 It has been known for several years that a (strong) correlation exists between the risk of developing ovarian cancer and infertility and menopause. Moreover, reference 5 and 6 are not really recent. Please rephrase this sentence.

P.3 Reference 3 has not shown this, only refers to other studies. Please refer to the original publications.

(Minor essential revision)

5. Materials and Methods

Microarray and PCR experiments – information concerning qPCR is too limited. Why did the authors chose for only these two genes and why these two genes and not genes from other families as well? Why was only one housekeeping gene included and not, as is usual 3 to 4.

(Minor essential revision)

6. Results and Discussion

I suggest the authors divide the text in a Result section and a Discussion section. The present Results and Discussion section is way too long and sometimes overlapping and confusing.

In the Materials and Methods and in the figures the authors describe that the SKOV-3 cells have been exposed to LH for different periods of times. The relevance of this time course is not discussed in the Results and Discussion section on the contrary, it is hardly mentioned. What was the purpose of this time course in LH exposure and which exposure time was used for the microarray analyses?

A control group, non-transfected SKOV-3 cells + LH is missing. There are studies that report that LH increases proliferation and invasiveness of untransfected SKOV-3 cells (ref. 35. 36).

(Major compulsory revision)

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.