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LETTER TO THE EDITOR

Reply: Improved understanding of very small embryonic-like stem cells in adult mammalian ovary

Sir,

We are grateful to Dr. Bhartiya and coworkers for their appreciation of our work and for providing appropriate suggestions for a better investigation in this field of research.

In agreement with our data in human ovaries (Silvestris *et al.*, 2018), they emphasize the existence of two distinct populations of stem cells in sheep ovaries, developmentally linked to each other (Bhartiya and Patel, 2017). In particular, this phenomenon is putatively explained by asymmetric cell divisions, which generate both small pluripotent stem cells and oocyte-like structures, that are characterized by differential expression of OCT4.

Similarly, we detected in the 'small-sized' population deriving from human ovarian surface epithelium cells, the expression of a primordial germline marker, namely DPPA3. This was lost after differentiation into 'large oocyte-like' cells which, contrarily, expressed GDF9 and SYCP3 as markers of maturity (Silvestris *et al.*, 2018). However, in our work we focused on the spontaneous maturation of $DDX4^{+}$ positive cells *in vitro*, since we postulated that, even in the absence of exogenous stimuli, ovarian stem cells (OSCs) would be able to generate oocyte-like cells in both pre- and post-menopausal women.

We agree with Bhartiya and coworkers that stimulation of these cells with follicle-stimulating hormone (FSH) should be performed to verify their observation (Patel *et al.*, 2018) on human samples, and find out if any difference exists in comparison with sheep ovaries. In this regard, we preliminarily verified the FSH receptor (FSHR) gene sequence on reference database (https://www.ensembl.org/index.html) and learned that, besides the canonical transcript (FSHR1), there are other transcript variants which should be further investigated for potential discrepancies between human and sheep species. We plan to explore these aspects to complete our work.

Such investigations, together with the comparative analysis of OCT4 expression (pre- and post-FSH treatment), would certainly improve our knowledge on the mechanisms underlying OSC maturation, and the role exerted by FSHR in this context.

References

Bhartiya D, Patel H. Ovarian stem cells-resolving controversies. *JARG* 2017. doi:10.1007/s10815-017-1080-6.

Patel H, Bhartiya D, Parte S. Further characterization of adult sheep ovarian stem cells and their involvement in neo-oogenesis and follicle assembly. *J Ovarian Res* 2018;**11**:3. doi:10.1186/s13048-017-0377-5.

Silvestris E, Cafforio P, D'Oronzo S, Felici C, Silvestris F, Loverro G. In vitro differentiation of human oocyte-like cells from oogonial stem cells: single-cell isolation and molecular characterization. *Hum Reprod* 2018. doi:10.1093/humrep/dex377.

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