Transcriptional Modifications in Cumulus Cells during Human Oocyte In vitro Maturation

Jesús Cadenas[1]; Cristina Subiran[1]; Lise B. Christensen[1]; Tanni K. Borgbo[1]; Stine G. Kristensen[1]; Claus Y. Andersen[2].

1. Laboratory of Reproductive Biology, The Juliane Marie Centre for Women, Children and Reproduction, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark.

2. Fertility Clinic, University Hospital of Copenhagen, Herlev and Gentofte Hospital, Herlev, Denmark.

It is widely acknowledged that the communication between the oocyte and the surrounding cumulus cells (CCs) is essential for oocyte maturation. However, the intricate details of this process in humans are not yet fully understood. Attempts have been made to define oocyte quality markers based on transcriptional changes in CCs from GV and MII oocytes after ovarian stimulation during IVF cycles or after in vitro maturation (IVM) with limited success. Nevertheless, the transcriptome of CCs from fresh unstimulated GV oocytes (before IVM) has never been compared with CCs from GV and MII oocytes after IVM to unravel transcriptional modifications in human CCs that may contribute to oocyte maturation in vitro.

In the present study, 25 CC samples were collected ex vivo from cumulus-oocyte complexes (COCs) located in the surplus medulla tissue of 8 patients (mean age 29 years; range 19-36) who underwent unilateral ovariectomy and ovarian tissue cryopreservation, including CCs from fresh GV COCs (before IVM, n=5) and CCs from MII and GV COCs after IVM (GV-IVM, n=8; and MII-IVM, n=12). Overall, 1763 differently expressed genes (DEGs) were significantly regulated between CCs from fresh GV (before IVM) and MII-IVM, being 1057 protein-coding genes, including upregulated DEGs such as *DHCR24, RUNX2, ANGPT2, WISP2, LHCGR*, and *IGF2*, and downregulated DEGs, such as *VIT, CRHBP, ACAN, AMH, FST*, and *VCAN*, among others. The top upregulated pathways included, VEGF-VEGR signaling, MAPK signaling, PPAR signaling, Wnt signaling, cholesterol metabolism, and fatty-acid beta-oxidation, while downregulated pathways included the mesodermal commitment pathway, TGF-beta signaling, PI3K-AKT signaling, endoderm differentiation, RANKL/RANK signaling, androgen receptor signaling and regulation of actin cytoskeleton, among others. When comparing CC from COCs that failed after IVM (GV-IVM) vs. MII-IVM, only 50 significant DEGs were detected, with 27 of them being protein-coding genes, 12 of which were upregulated and 15 downregulated. *PBX1* was the only unique upregulated DEG, whereas unique downregulated DEGs included *SORL1, TANC1, ERG, CCDC3, IQGAP1,* and *SUN1*. All the remaining DEGs were also differently expressed between fresh GV and MII-IVM. These findings may improve the current knowledge of key human oocyte maturation regulators and help uncover the mechanisms of ovarian function and dysfunction. This can potentially lead to better IVM outcomes and make more competent oocytes available for fertility treatment.