Gene expression profiling of cumulus cells in polycystic ovarian syndrome patients: A systematic review and integrated bioinformatic analysis

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ABSTRACT

Introduction: Polycystic Ovarian Syndrome (PCOS) is a hormonal disorder affecting reproductive function, which often emerges in the early menstrual cycles or develops later throughout the reproductive years. PCOS common symptoms include irregular menstrual cycles, hyperandrogenism, as well as polycystic ovaries, albeit the symptoms may vary among individuals due to underlying genetic and environmental influences. Impaired reproductive functions, including hormonal regulation in PCOS, are often linked to altered gene expression within the cumulus cells that surround the oocyte, potentially leading to anovulation, where ovulation fails to occur, thus compromising fertility. Hence, this study aims to identify genes that are differentially expressed in the cumulus cells among infertile women with PCOS and the pathways involved. **Materials and Methods:** An extensive literature search was conducted employing EBSCOhost, PubMed, ScienceDirect, and Scopus databases to systematically identify gene expression profiles in cumulus cells and elucidate the molecular pathways implicated in the pathogenesis of PCOS. Terms including ("Infertile women" OR Infertility OR Subfertility OR Sterility) AND (PCOS OR "Polycystic ovarian syndrome" OR "Polycystic ovary syndrome") AND ("Cumulus cells" OR "Cumulus granulosa cells" OR "Granulosa cells" OR Cumulus) AND ("Gene expression" OR Profiling OR Transcriptome OR Transcriptomic) were used as the keywords in abstract field. Bioinformatics methodologies used were Venn diagram to identify overlapping DEGs, STRING to elucidate protein–protein interaction networks, and DAVID for comprehensive functional annotation and pathway enrichment analysis. **Results:** Two hundred and twenty-six studies were retrieved, and all studies were screened according to the inclusion and exclusion criteria. After the screening, fourteen studies were selected, and eleven differentially expressed genes (DEGs) reported by at least two papers were extracted from the studies. The integrated bioinformatic analysis using DAVID and STRING revealed a protein-protein interaction (PPI) network with two intermolecular interaction clusters. Based on the Gene Ontology (GO), most DEGs were localised in the extracellular space (GO:0005615), suggesting the involvement of these genes in modulating intercellular signalling of cumulus cells for oocyte maturation prior to fertilisation. The genes GDF9, TGFB1, INHBB, BMPR1A, and BMP15 participated in the cytokine-cytokine receptor activity (hsa04060), while GDF9, TGFB1, INHBB, and BMP15 were involved in the growth factor activity (GO:0008083). Correspondingly, TGFB1 and BMPR1A were also involved in the positive regulation of epithelial cell proliferation (GO:0050679) alongside RUNX2, proposing their role in promoting cell proliferation during follicular development. Another cluster consists of LHCGR, CYP11A1, and CYP1B1, which participated in the ovarian steroidogenesis (hsa04913) as well as in the cellular response to luteinizing hormone stimulus (GO:0071373), implying their role in regulating sterol metabolic process (GO:0016125) required in hormonal homeostasis, which is critical for proper reproductive functions. **Conclusion:** This systematic review identified key DEGs, including GDF9, TGFB1, INHBB, BMPR1A, BMP15, RUNX2, LHCGR, CYP11A1, and CYP1B1, that are critically involved in folliculogenesis, steroidogenesis, and signalling pathways essential for oocyte maturation. The dysregulation of these genes' expression underscores a disrupted follicular microenvironment, unravelling the compromised reproductive mechanisms. Hence, these findings enlighten a focused molecular framework for therapeutic strategies aimed at improving reproductive outcomes in PCOS patients.

Keywords: Infertility, In vitro fertilisation, gene expression, PCOS