Differential gene expression in cumulus cells between reproductive age and advanced maternal age women: A systematic review and bioinformatic pathway analysis

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ABSTRACT

Introduction: Female reproductive potential declines with age, primarily due to reduced oocyte quality. Cumulus cells (CCs), which surround and support the oocyte, mirror its microenvironment and play a critical role in regulating oocyte maturation and competence. Exploring gene expression patterns in CCs offers a noninvasive window into the molecular mechanisms underlying reproductive ageing. This study aimed to identify differentially expressed genes (DEGs) in cumulus cells between reproductive-age and advanced maternal age (AMA) women and to determine the pathways influenced by ageing in cumulus cells. **Materials and Methods:** This systematic review was conducted in accordance with PRISMA guidelines. A comprehensive literature search was performed using EBSCOhost, Science Direct, PubMed, and Scopus for articles published up to 11 July 2025. Search terms were developed using Medical Subject Headings (MeSH) from the Cochrane Library and refined through analysis of relevant articles. The search strategy included the following keywords: ("cumulus cell" OR "granulosa cell" OR cumulus) AND (age OR "advanced maternal age" OR "maternal age" OR ageing) AND ("gene expression" OR profiling OR transcriptome OR transcriptomic). Eligible studies were clinical human studies that compared cumulus cell gene expression between reproductive-age and AMA women. Protein–Protein Interaction (PPI) network analysis, clustering, and visualization were performed using STRING. Gene Ontology (GO) and pathway enrichment analyses were conducted using the DAVID database. **Results:** Out of 186 retrieved articles, seven clinical human studies published between 2010 and 2022 met the inclusion criteria. These studies employed qPCR, microarray, or RNA sequencing to compare gene expression in cumulus cells between younger and AMA women. In total, 32 differentially expressed genes (DEGs) were identified as consistently reported in at least two studies. Bioinformatic clustering analysis of the DEGs revealed four major gene clusters. The first cluster showed enrichment in genes involved in gene expression regulation, cell migration, and apoptosis, with notable links to the diabetic cardiomyopathy pathway. The second cluster highlighted genes involved in the detoxification of reactive oxygen species, suggesting increased oxidative stress in the ageing ovarian environment. These findings support the hypothesis that reproductive ageing is associated with specific gene expression changes in cumulus cells that impact oocyte quality through multiple biological pathways. **Conclusion:** This systematic review and integrated bioinformatic analysis identified consistent gene expression alterations in cumulus cells associated with advanced maternal age. Key affected pathways include oxidative stress response, apoptosis, and cellular signaling, which may contribute to the decline in oocyte quality among older women. The findings suggest that transcriptomic profiling of cumulus cells holds potential for identifying non-invasive biomarkers and therapeutic targets to improve fertility outcomes in ageing women. This study advances our understanding of the molecular mechanisms underlying reproductive ageing and supports the development of integrative approaches for reproductive health in the context of healthy ageing.

Keywords: Ageing, cumulus cells, gene expression, gene ontology