Micrornas regulate expression of aged human cumulus cells genes that are essential for oocyte quality

Abstract

Objective

To evaluate the impact of female aging on the gene expression profile of human cumulus cells (CCs) and to characterize the biological relationships between microRNAs (miRNAs) and impacted CC-genes by aging.

Design

This study includes 47 CCs isolated from mature MII oocytes collected from patients aged <30 years, 31-36 years, and 37-43 years (n=33). All groups of CCs were obtained from patients who underwent COS for male infertility for ICSI.

Materials and Methods

CCs from each MII oocyte were analyzed individually using whole genome U133 Plus 2.0 GeneChip Affymetrix microarrays. Significance analysis of microarray was used to analyze the data according to age of patients. Using deep-sequencing technology, we dissected the microRNome of pooled CCs (n=20). The correlation between miRNAs and their corresponding mRNA targets was analyzed using in silico prediction algorithms. Validation was performed by qPCR.

Results

2,405 genes were differentially expressed among the three groups according to age. In CCs collected from patients >37 years, angiogenic genes including FGF2 (x3.2, FDR=0) were significantly over-expressed. Whereas, genes related to insulin signaling pathway were overexpressed in CCs of patients (31-36

years), like IGFBP3 (x2.0, FDR=0.004). Furthermore, some of the genes whose down regulation in CCs was previously shown to be associated with oocyte aneuploidy such as (TP53 and SPSB) were down-regulated in older CCs. A bioinformatics analysis was performed to identify the miRNAs that are putative regulators of the differentially expressed genes of the study. It revealed that the pathways impacted by age were potential targets of specific miRNAs identified in our CCs small RNAs sequencing. MIR202 is a potential regulator of the hyaluronan synthase-encoding gene HAS2 that is related to aging and angiogenesis. IGFBP3 was target of MIR210, whereas FGF2 was targeted by MIR424.

Conclusion

The present study reports for the first time an extensive analysis of gene expression in CCs in relation to female age. Our findings point to aging as a major player in processes and pathways that are of key biological importance for oocyte growth and genome integrity. The characterization of the miRNA regulators of the genes impacted by female age represents a valuable resource for future investigations on the biology of aging and aneuploidy oocyte.