Maternal age affects insulin signaling pathway and angiogenic factors of human cumulus cells: importance of MIR-21 and MIR-140

Abstract

Objective

To evaluate the impact of maternal aging on the gene expression profile of human cumulus cells (CCs) and to characterize the biological relationships between miRNAs and the CC-genes according to maternal age.

Design

This study includes 43 CCs isolated from mature MII oocytes collected from patients aged <30 years (24-29 years) and 42 CCs from patients aged ≥30 years (30-42 years).

Materials and Methods

CCs from each MII oocyte were analyzed individually using whole genome U133 Plus 2 GeneChip Affymetrix microarrays. Significance analysis of microarray was used to analyze the data according to age of patients with 1.5 fold cut-off and false discovery rate <5%. 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

370 genes were differentially expressed (FC ≥1.5, FDR <0.05) between the two groups according to age. In CCs collected from patients > 30 years, the angiogenic factors that are known to play an important role in the human pre-ovulatory and oocyte

competence, including SPP1 (4.2, p= 0.0001) and chemokine genes CCL2 (2.9, p= 0.003), CCL20 (2.3, p= 0.009) which is regulated by MIR-21, were down-regulated. Conversely, genes related to insulin signaling pathway were up-regulated such as INSR (2.3, p= 0.0001), IGFBP3 (1.8, p= 0.0001) and IGFBP5 (1.7, p= 0.0001) which is regulated by MIR-140. Interestingly, a set of transcriptional genes involved in particular stress responses were preferentially expressed in CCs-collected from patients > 30 years. Among these genes MSRB3 (1.8, FDR=0.0001) plays a protective role during oxidative stress.

Conclusion

This study reveals that the expression of genes and miRNAs involved in angiogenesis and insulin signaling pathway are affected in CCs with maternal age and probably explain why there is an increase in oocyte aneuploidy with age due to oxidative stress.