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Title
GRANULOSA CELL METABOLISM IS DIFFERENTIALLY IMPACTED BY OBESITY AND AGING AND CORRELATED WITH OOCYTE COMPETENCE.

ATSUSHI MORIMOTO[1,2], RYAN ROSE[3], KIRSTEN SMITH[1],
DOAN THAO DINH[1], TAKASHI UMEHARA[2], YASMYN WINSTANLEY[1],
DARRYL RUSSELL[1], REBECCA ROBKER[1]

1. ROBINSON RESEARCH INSTITUTE; THE UNIVERSITY OF ADELAIDE, SA AUSTRALIA
2. HORAC GRAND FRONT OSAKA CLINIC; IVF JAPAN GROUP, OSAKA JAPAN
3. GENEA - FERTILITY SA, SA AUSTRALIA
4. HIROSHIMA UNIVERSITY, HIROSHIMA JAPAN

Background and Aims: Aging and obesity are associated with female infertility, with mitochondrial dysfunction proposed as an underlying factor; but our understanding of energy metabolism within the ovary remains limited.

Method: This study focused on the granulosa cells surrounding the oocyte and investigated mitochondrial function, glycolytic function, total ATP production, and fatty acid metabolism using real-time metabolic analysis (Seahorse XFe96) to understand the effects of obesity and aging on energy metabolism. Mouse models were used to precisely isolate the effects of aging and obesity, with parallel studies conducted on human granulosa cells.

Results: In mice, aging impaired both mitochondrial function and glycolytic function, while obesity primarily reduced mitochondrial function. Mice with both aging and obesity showed massively impaired granulosa cell metabolism. Next, the metabolic profile of granulosa cells in the follicular fluid of a cohort of 130 women who underwent IVF/ICSI cycles was measured. Aging primarily impaired mitochondrial function, with ATP production biased towards glycolysis, and no correlation was found with glycolytic function. Obesity primarily affected ATP production efficiency in mitochondria. Correlations between granulosa cell energy metabolism and embryonic development were also found. Mitochondrial spare capacity was associated with more retrieved oocytes, glycolytic reserve capacity was associated with Day 3 embryo quality, and mitochondrial ATP production was associated with improved blastocyst formation rates. Analysis of patient diagnoses revealed that in patients with normal ovarian function, only ATP production efficiency was decreased by aging, whereas in patients diagnosed with conditions of impaired ovarian function, mitochondrial function was more important. Interestingly, patients with adequate mitochondrial function showed good embryonic development, whereas those with very high mitochondrial and glycolytic energy metabolism showed a negative correlation with embryonic development, which was also observed in patients with ovarian dysfunction**.**

Conclusion: These results provide new insights into the underlying metabolic dysfunction that occurs with female infertility.