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Short Communication

Cytoplasmic Communication between Oocytes and Granulosa Cells during Controlled Ovarian Stimulation

Elena Moravec*

Department of Reproductive Biology, North Danube University, Bratislava, Slovakia

DESCRIPTION

Controlled ovarian stimulation remains one of the most discussed procedures in assisted reproduction because ovarian response differs widely among patients even when similar medication schedules are used. Research during the last decade has shown that communication between oocytes and granulosa cells influences follicular growth, meiotic activity, and metabolic balance during stimulation cycles [1]. This cellular interaction occurs through direct contact, secreted signaling molecules, and transfer of small metabolites that support oocyte maturation. Better understanding of these exchanges may support the development of refined stimulation methods with improved embryo competence and reduced cycle cancellation rates [2].

Granulosa cells surround the oocyte from the earliest follicular stages and continue to influence its development until ovulation. Gap junctions connect the oocyte and neighboring granulosa cells, allowing transport of amino acids, ions, nucleotides, and regulatory molecules. Cyclic adenosine monophosphate and cyclic guanosine monophosphate participate in meiotic arrest before the luteinizing hormone surge. During stimulation protocols using follicle stimulating hormone analogs, granulosa cell metabolism changes rapidly. Increased glucose uptake and steroid production create a microenvironment that can either support or impair oocyte quality depending on hormone concentration, patient age, and ovarian reserve [3].

Recent laboratory investigations have indicated that granulosa cells regulate mitochondrial activity inside the oocyte through exchange of metabolites such as pyruvate and lactate. Oocytes have limited glycolytic activity and therefore depend heavily on surrounding cells for energy substrate conversion. When granulosa cells display impaired mitochondrial function, the oocyte often shows reduced developmental competence after fertilization [4]. This relationship has attracted attention in women with diminished ovarian reserve and in patients with repeated implantation failure after transfer of morphologically acceptable embryos.

Researchers from several reproductive centers have examined follicular fluid composition during stimulation cycles. Variations in lipid concentration, oxidative markers, and inflammatory mediators appear to correlate with embryo development patterns. In women with polycystic ovarian syndrome, elevated androgen levels inside follicles may alter granulosa cell signaling and interfere with meiotic progression [5]. Some reports describe abnormal expression of growth differentiation factor 9 and bone morphogenetic protein 15 in these patients. Since both proteins contribute to follicular communication, altered expression may partly explain lower rates of mature oocyte retrieval despite large follicle numbers in some cycles. The influence of age on cytoplasmic communication has also received increasing attention. Aging ovaries often contain granulosa cells with shortened telomeres and altered mitochondrial Deoxyribonucleic Acid (DNA) copy numbers. These cellular changes can influence steroid synthesis and antioxidant defenses. Oocytes retrieved from older patients frequently demonstrate spindle abnormalities and chromosomal segregation errors. Although maternal age remains a dominant factor affecting reproductive outcome, studies suggest that local follicular communication may contribute to age-associated decline beyond chromosomal instability alone [6-8].

Controlled stimulation protocols vary considerably between clinics. Gonadotropin releasing hormone agonist and antagonist approaches produce different endocrine conditions during follicular recruitment. Some investigators propose that mild stimulation schedules may preserve more physiologic communication between oocytes and granulosa cells. High gonadotropin exposure has been associated in some reports with altered gene expression in cumulus cells, particularly genes related to apoptosis and oxidative stress. However, evidence remains inconsistent because patient populations, laboratory conditions, and stimulation goals differ among studies. Cumulus cells collected during intracytoplasmic sperm injection procedures have become valuable material for molecular analysis. Messenger Ribonucleic Acid (RNA) profiles from these cells may provide indirect information regarding oocyte competence. Certain transcripts related to cell cycle control, steroid

Correspondence to: Elena Moravec, Department of Reproductive Biology, North Danube University, Bratislava, Slovakia, E-mail: elena.moravec.ndu@biocaremail.com

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metabolism, and inflammatory signaling have shown association with blastocyst formation and implantation outcome. Artificial intelligence models are now being explored to combine transcriptomic findings with embryology data and hormone measurements. Such approaches may eventually improve embryo selection without direct embryo biopsy [9].

Oxidative stress continues to be an important concern during ovarian stimulation. Reactive oxygen species are produced naturally during cellular metabolism, though excessive accumulation may damage DNA, lipids, and proteins. Granulosa cells contain antioxidant enzymes that help maintain balance within the follicular environment. Reduced antioxidant capacity has been reported in women with endometriosis, obesity, and advanced reproductive age. Several clinics have investigated nutritional supplementation before *In Vitro* Fertilization (IVF) treatment, including coenzyme Q10, melatonin, and vitamin D. Clinical outcomes remain variable, but some studies describe improved oocyte maturity and embryo development in selected patient groups.

Genetic variation among patients may further explain differing responses to stimulation medication. Polymorphisms involving follicle stimulating hormone receptors and luteinizing hormone receptors have been linked to altered ovarian sensitivity [10]. Women carrying specific receptor variants may require adjusted gonadotropin doses to achieve adequate follicular recruitment. Investigation into granulosa cell signaling pathways may contribute to individualized stimulation planning based on genetic background rather than age and ovarian reserve markers alone.

CONCLUSION

Despite major progress in reproductive medicine, many aspects of oocyte-granulosa cell interaction remain poorly understood. Human follicles contain dynamic cellular networks influenced by endocrine signals, genetic background, metabolism, age, and environmental conditions. Controlled ovarian stimulation modifies these relationships in ways that are still being studied. Continued investigation into cytoplasmic communication may contribute to safer stimulation methods, improved embryo quality, and reduced emotional and financial burden for couples seeking assisted conception.

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