Oocyte environment: follicular fluid and cumulus cells are critical for oocyte health

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Bidirectional somatic cell–oocyte signaling is essential to create a changing intrafollicular microenvironment that controls primordial follicle growth into a cohort of growing follicles, from which one antral follicle is selected to ovulate a healthy oocyte. Such intercellular communications allow the oocyte to determine its own fate by influencing the intrafollicular microenvironment, which in turn provides the necessary cellular functions for oocyte developmental competence, which is defined as the ability of the oocyte to complete meiosis and undergo fertilization, embryogenesis, and term development. These coordinated somatic cell–oocyte interactions attempt to balance cellular metabolism with energy requirements during folliculogenesis, including changing energy utilization during meiotic resumption. If these cellular mechanisms are perturbed by metabolic disease and/or maternal aging, molecular damage of the oocyte can alter macromolecules, induce mitochondrial mutations, and reduce adenosine triphosphate production, all of which can harm the oocyte. Recent technologies are now exploring transcriptional, translational, and post-translational events within the human follicle with the goal of identifying biomarkers that reliably predict oocyte quality in the clinical setting. (Fertil Steril® 2015;103:303–16. ©2015 by American Society for Reproductive Medicine.)

Key Words: Oocyte, cumulus cells, follicular fluid, oxidative stress, metabolomics

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Human follicle development involves multiple intraovarian and endocrine interactions that create a changing intrafollicular microenvironment for optimal oocyte development. Bidirectional somatic cell–oocyte signaling via paracrine interactions regulates primordial follicle growth into a cohort of growing follicles, from which one antral follicle is selected to ovulate a developmentally competent oocyte, which is defined as the ability of the oocyte to complete meiosis and undergo fertilization, embryogenesis, and term development (1).

According to the Society of Assisted Reproductive Technology, of 165,172 assisted reproductive cycles performed in 2012, only 40.6% of fresh nondonor IVF cycles in women less than 35 years of age lead to a live birth, with an embryo implantation rate of only 37.4% (2). Of these live births, 30.5% were multiple fetal pregnancies. Chromosomal screening of blastocysts and frozen ET techniques have increased IVF-related implantation rates to 65%–71% (3–5). Continued embryo implantation failure, however, implies that other factors also affect oocyte quality, perhaps through complex intrafollicular processes that control the nuclear and/or cytoplasmic maturation of the oocyte. Since less than 7% of oocytes retrieved by IVF develop into a normal embryo that yields a live birth (6), a search for improved predictors of oocyte quality has focused on ovarian cellular signalling and metabolism, particularly since metabolic disease and maternal aging adversely affect cumulus-oocyte complex (COC) interactions (7, 8). This paper discusses what processes normally occur during oocyte development, how they are perturbed by various clinical conditions, and why understanding these homeostatic mechanisms may improve pregnancy outcome by IVF and diminish the multiple-birth rate by transferring fewer embryos into the uterus.

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SOMATIC CELL–OOCYTE INTERACTIONS

From an oocentric point of view, the oocyte plays an important role in determining its own developmental fate. Throughout folliculogenesis, oocyte-derived proteins of the transforming growth factor-β (TGFβ) superfamily (most notably, bone morphogenetic protein 15 [BMP15] and growth differentiation factor 9 [GDF9]) interact with surrounding somatic cells, which in turn produce their own paracrine factors (i.e., kit ligand, activins, inhibins, antimüllerian hormone [AMH], TGFα), to coordinate oocyte growth, granulosa cell proliferation, and theca cell differentiation (9–12). This bidirectional somatic cell–oocyte signaling continuously changes over time to synchronize follicle development with oocyte maturation (Fig. 1).

STEROIDOGENESIS

Steroidogenesis is crucial for the synchronization of follicle growth and oocyte development, beginning with uptake of cholesterol from circulating lipoproteins and storage of cholesterol as esters in cellular lipid droplets (14–17). Ovarian cellular cholesterol initially is transported into mitochondria via the steroidogenic acute regulatory protein. Once inside, side-chain cleavage cytochrome P-450 ($P450_{scc}$) converts cholesterol to pregnenolone (P5) (18), which then is converted by either 17 a-hydroxylase/17–20 lyase (P450c17) to 17-hydroxypregnenolone (17-OHP5), DHEA, and sex steroids; or 3-beta-hydroxysteroid dehydrogenase (3βHSD) to progesterone (P_4; Fig. 1) (19).

Androgen produced through this sex steroid pathway can act through its own receptor (20) to promote preantral and small antral follicle growth (21, 22) by increasing gene expression of FSH receptor, insulin-like growth factor (IGF)-I receptor, and IGF-I (23, 24) in granulosa cells, as well as IGF-I and IGF-I receptor in oocytes (25). These androgen receptor–mediated events allow the growing follicle to interact with FSH, growth factors, and oocyte-derived factors (26–29) to promote granulosa cell differentiation into mural and cumulus cell layers separated by a fluid-filled antrum (30). Within the antral follicle, androgen produced from LH-stimulated theca cells is then aromatized to estrogen by FSH-stimulated granulosa cells (31, 32). This two-cell steroidogenic process, facilitated by granulosa cell–derived paracrine factors (i.e., inhibins and IGF1 and follistatin) that promote theca cell $P450_{c17}$ activity (33, 34), allows sufficient aromatizable androgen production for continuous E_2 synthesis, despite declining serum FSH levels with follicle growth (31).

E_2 is crucial for proper oocyte development because immature human oocytes have E_2-dependent, calcium-mediated mechanisms of cytoplasmic maturation that are susceptible to androgen inhibition (35–37). Specifically, T inhibition of meiotic maturation and embryonic development is greater in cumulus-denuded than in cumulus-enclosed mouse oocytes matured in vitro, suggesting that cumulus cells protect the enclosed oocyte against hyperandrogenism through local aromatase activity (38, 39). This finding agrees with immature human oocytes from small, hyperandrogenic polycystic ovary syndrome (PCOS) follicles that have decreased rates of in vitro maturation, fertilization, and embryo development compared with immature oocytes from normal women (40, 41). Conversely, high intrafollicular E_2/androgen ratios are associated with successful IVF-related pregnancy outcome (42), while low E_2 production in IVF patients with 17α-hydroxylase deficiency is accompanied by in vitro embryonic developmental arrest (43).

FIGURE 1

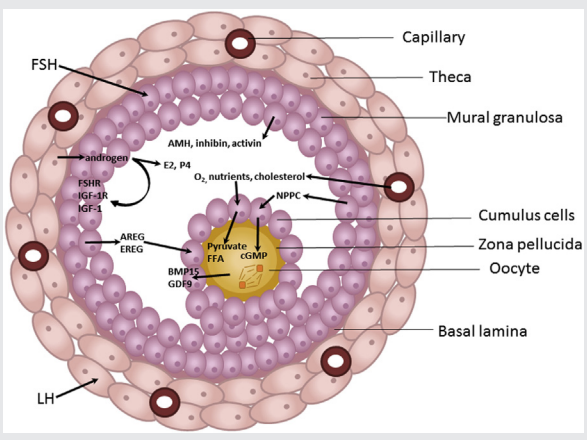

Diagram of an ovarian preovulatory follicle depicting how somatic cells influence oocyte competence via steroidogenesis, cellular signaling, and metabolism. Adapted from Krisher (13). Abbreviations: AREG = amphiregulin; BMP15 = bone morphogenetic protein 15; EREG = epiregulin; FSHR = FSH receptor; IGF-1R = IGF-1 receptor; NPPC = natriuretic peptide precursor type C; O_2 = oxygen.

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OOCYTE MATURATION

Before ovulation, the germinal vesicle– (GV-) stage oocyte is arrested in meiotic prophase I through high oocyte cyclic adenosine monophosphate (cAMP) levels (44). To maintain meiotic arrest, granulosa cells produce natriuretic peptide precursor type C (NPPC) that binds NPPC receptors (NPR2) on cumulus cells, resulting in the production of cyclic guanosine monophosphate (cGMP), which then transfers to the oocyte via gap junctions to inhibit phosphodiesterase 3A (PDE3A), thereby preventing hydrolysis of cAMP (44–46).

With the midcycle LH surge or hCG administration, meiotic inhibition is overridden by lowering total follicular cGMP content, closing gap junctions, which results in a fall in oocyte cAMP, and increasing synthesis of granulosa cell–derived epidermal growth factor– (EGF-) like proteins (amphiregulin, epiregulin, and betacellulin) (46–48). By interacting with oocyte-derived factors (44, 48, 49), EGF-like proteins activate the EGF receptor to engage the MAPK pathway for meiotic resumption, with COC expansion in response to cyclo-oxygenase 2 (COX2), gremlin1 (GREM1), hyaluronic acid synthase 2 (HAS2), and pentraxin 3 (PTX3) as down-stream GDF-9 target genes (46, 50). The net result is an oocyte that can undergo GV breakdown to produce a haploid