Let's Talk and Grow Together: A Bidirectional Communication between Granulosa- and Oocyte-Derived Factors in the Ovary

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Abstract

Reproduction, one of the most active and appealing area of research for endocrinologists and reproductive biologists since many a years, has several faces that remains to be unmasked in terms of its regulatory aspects. Available information on the regulation of oocyte development and maturational competence are gaping and needs elucidation to achieve utmost quality of eggs, a major area of concern. The notion of the somatic follicular cells providing an appropriate microenvironment for the development of oocyte throughout its journey has been replaced with the current perception of a complex yet regulated cross-talk between the granulosa- and oocyte-derived factors to orchestrate follicle development. Interestingly, actions of FSH and LH are mediated or modulated by these locally produced non-steroidal peptide factors from the follicular layer and the oocyte itself (insulin-like growth factors (IGFs), epidermal growth factor (EGF) family members, TGFβ super family members etc.), forming an intimate regulatory network within the ovarian follicles. Present article will provide a deeper insight into the need and underlying mechanisms of action of these growth factors in the intraovarian network to sustain a healthy oocyte.

Keywords: Oocyte; Follicular layer; Theca; Granulosa; Growth factors; IGF; IGFR; EGF; EGFR; Maturational competence

Introduction

In the present scenario of environment and its associated external factors, reproduction seems to pave new ways out for maintaining intimate, well-organized axes to help an organism develop its gamete of utmost quality and undergo positive successful fertilization. Achieving high quality eggs is a major area of discussion and research for the fact that there still remains major gap in the molecular and physiological mechanisms underlying the production of such eggs. Considering the importance of intelligently designed oocyte for a female and the negative consequences that may occur due to impairment of the complex dialogue between neuro-endocrine, endocrine and locally produced autocrine/paracrine factors within the ovarian follicles, the indispensable signaling pathways involved in producing such a maturationally competent oocyte need to be unravelled. An oocyte is the mother of existence and is nursed upon by its surrounding follicular layer till the point it reaches the ability to mature. However, the concept of the oocyte as a passive partner, subjected to control by the follicle cells, is no longer plausible and recent evidences have pointed towards the participation of granulosa- and oocyte-derived non-steroidal peptide factors in modulating functions of each other indicating the existence of a bidirectional communication between both the compartments. Though it is well-known that follicular growth and oocyte maturation are dependent primarily on pituitary-derived gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), pictures emerging from recent studies have put forward the potential involvement of these local factors, more specifically growth factors, to integrate with endocrine inputs and control ovarian and follicle development [1,2]. These factors include (but not limited to) mainly insulin-like growth factors (IGFs) [3-5], epidermal growth factor (EGF) family members, TGFβ super family members etc., forming an intimate regulatory network within the ovarian follicles. Present article will provide a deeper insight into the need and underlying mechanisms of action of these growth factors in the intraovarian network to sustain a healthy oocyte.
Though IGFs have shown to have cardinal influence in most other organ systems, information on ovary as a major site of IGF synthesis, reception and action is from recent past [13]. All components of the somatotrophic axis, including GH, IGFs and their receptors are expressed in the ovary of both mammals and fish [4,14,15] suggesting the existence of an intra-ovarian GH-IGF mini-axis in vertebrates [16]. PI3K activation has been implicated in growth factor-induced resumption of meiosis in mammalian, amphibian and teleost oocytes [17-19]. The action of PI3K on oocyte is mediated via downstream Akt/PKB that in turn regulates multiple cellular changes including cell polarization, re-entry into cell cycle, cell survival and oocyte maturation [20]. Active Akt/PKB is sufficient to promote oocyte maturation through oocyte-specific PDE3, the enzyme that degrades and inactivates cAMP [18,19]. Several earlier studies have also reported activation of MAPKs during IGF stimulation of meiotic maturation that involves the participation of GTP-binding protein, p21 Ras and serine/threonine kinase Raf [21]. Since its detection in vertebrate ovary, several studies have been conducted to identify the physiological significance of IGF system in regulating ovarian function under normal as well as pathological condition [22]. In mammals, IGFs role in reproduction includes modulation of steroidogenesis, oocyte maturation, follicular growth and survival of growing oocytes [14]. IGF1 enhances FSH-stimulated progesterone accumulation rat granulosa cells [23]. While granulosa cells appear to be the site of IGF1 gene expression [24], in rat ovary, expression of type-I IGF receptor has been reported in both granulosa [25] and theca-interstitial cells [26]. In mouse targeted null-mutation of the IGF1 gene results in infertility, secondary to failure to ovulate even after administration of gonadotropins [27]. Interestingly, earlier decades have even evidences of existence of well-coordinated IGF system in human, rodent and primate uterus, with its expression being regulated by sex steroids suggesting its role in modulating the proliferative effects of sex steroids [28-30]. So far as studies in sub-mammalian vertebrates specifically in fishes are concerned, IGF1 and/or IGFII have been shown to act as potent regulators of oocyte maturation in red seabream [31], mummichog [32] and shortened eel [33]. In zebrafish, IGF1 acts synergistically with maturation-inducing steroid (17,20β-P) to overcome the estradiol inhibition of oocyte maturation [34]. Further, IGFIII, a gonad-specific follicular IGF ligand reported in zebrafish, has been documented to mediate gonadotropin-induced meiosis resumption [6]. Epidermal growth factor (EGF) family is yet another candidate recognized as the essential mediator of LH action on oocyte maturation in mammals [7,35]. Pre-ovulatory surge in LH promotes expression of EGF-like ligands including amphiregulin (AREG), epiregulin (EREG) and betacellulin (BTC) in mural granulosa cells and that of EGF receptor (EGFR) is concomitantly enhanced by oocyte-derived paracrine factors such as bone morphogenetic protein 15 (BMP15) and growth differentiation factor 9 (GDF9) [8]. As a result, MAPK (ERK1/2) activity is dramatically increased, thereby phosphorylating the gap junctions [36] and initiating the meiotic resumption in the oocyte [7,8,37] (Figure 1).

![Figure 1: Intra-ovarian network of local growth factors: site of action and indispensable follicular functions.](image-url)
Further, FSH regulation of Egfr expression in granulosa cells corroborates well with cumulus expansion and oocyte maturation in mouse ovary [38]. However, unlike the situation in mammals, zebrafish ovary depicts a beautiful case of bidirectional communication wherein the members of EGF family, with BTC as exception, are secreted exclusively from the oocyte. These ligands, primarily EGF and TGFα, upon receptor (EGFR) binding on follicular cells promotes activation of MAPK and synthesis of activins, which in turn act on the oocyte, activates Smad proteins and promote oocyte maturation [39,40]. Apart from its role in oocyte maturation through closure of gap junctions between cumulus cells and oocyte, EGFR has also been reported to trigger steroidogenesis in mammals, but the underlying mechanisms are not well-defined [35]. As mentioned earlier, oocytes do not merely reside inside the follicles and passively receive signals from follicular compartment, but it do dictate follicular cell differentiation and function for their own want via the local secretion of potent growth factors, termed as oocyte-secreted factors [41]. Oocyte- derived factors, primarily GDF9 and BMP15, belong to the TGF-β super family. GDF-9 and BMP-15 are specifically expressed by oocytes of all mammalian species from the first stages of follicle development to ovulation [42,43], suggesting their potential involvement in follicle development. These members of TGF-β superfamily regulate gene expression by binding to and phosphorylating type-I and type-II receptors that in turn activate Smad1/5/8, forms a complex with Smad4 and translocates to nucleus to exert its function [44]. Studies in the human follicle cells have suggested that GDF9 and BMPs interact with pituitary gonadotropins to inhibit StAR expression and progesterone synthesis thereby preventing premature luteinization [45,46]. The absence of GDF-9 at the one-layer thick primary follicle results in blockage in folliculogenesis, potentially through failure in thecal cell expansion, leading to compromised oocyte quality [47]. Though BMP-15 null mice do not show gross defects in ovarian morphology and may not be obligatory during pre-antral folliculogenesis, in absence of BMP-15 the animals are subfertile, considered secondary to decreased ovulation and fertilization rates [48]. Interestingly, expression levels of BMP-15 and GDF-9 tends to be higher in women with polycystic ovary syndrome [49], implicating the role of these oocyte-secreted factors in female reproductive pathology. On the contrary, studies in zebrafish revealed that BMP-15 has negative influence on oocyte maturation [50].

Discussion

Though at the cellular level these local autocrine/paracrine regulators, possibly act under the influence of pituitary Gth, their mechanism of action in the intraovarian network, their changing roles during ovarian development and interplay among themselves as well as their interactions with the endocrine hormones and/or the steroidal factors needs further elucidation. Any deregulation in these growth factor-mediated intra-follicular and/or intra-oocyte signaling cascades may lead to perturbation of ovarian functions and high risk of infertility and reproductive pathologies. Working with well characterized emerging models, e.g. zebrafish, would surely unveil the underlying molecular mechanisms required for development of maturationally competent eggs and may help establish a new path for improving fertility and treatment of ovarian disorders in vertebrates.

Conclusion

Thus an intimate intraovarian meshwork of factors derived from both follicular layer and oocyte forms the basis of a cross-talk between these compartments to sustain a balanced microenvironment, which in its turn helps in establishing the essence of bidirectional oocyte-follicular cell dialog.

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