—Mini Review—

Luteinizing Hormone-induced Ovarian Paracrine Factors for Oocyte Maturation

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Abstract: *Optimal maturation of oocytes and successful development of preimplantation embryos is essential for reproduction. Mammalian oocytes remain dormant in the diplotene stage of prophase I until the resumption of meiosis characterized by germinal vesicle breakdown (GVBD) following preovulatory gonadotropin stimulation. In response to the preovulatory luteinizing hormone (LH) increase, oocytes undergo GVBD, followed by first polar body extrusion. Although the preovulatory surge of LH is the primary event responsible for the induction of maturation of the oocyte, LH does not act directly on the oocyte due to the absence of functional LH receptors in germ cells. Instead, actions of LH are mediated either by paracrine factors secreted by LH-responsive somatic cells or by the transport of cellular messengers from granulosa/cumulus cells to oocytes through intercellular gap junctions. In addition to the nuclear maturation exemplified by GVBD and extrusion of the first polar body to complete the first meiotic division, oocytes also undergo cytoplasmic maturation characterized by cytoplasmic changes essential for monospermic fertilization, processing of the sperm, and preparation for development to preimplantation embryos. In this review, we summarize our recent works on the identification and characterization of novel LH-inducible ovarian factors for nuclear and cytoplasmic maturation of oocytes.*

Key words: *Luteinizing hormone, Maturation, Oocyte, Paracrine factor*

Introduction

In mammalian developing follicles, primary oocytes enter meiosis but are arrested at the diplotene stage of prophase I. The oocytes stay in this dormant state for months and years until they are about to be ovulated. In response to the preovulatory luteinizing hormone (LH) increase, the large nucleus of the oocytes (called the germinal vesicle, GV) in preovulatory follicles undergoes GV breakdown (GVBD), followed by first polar body extrusion. Although the preovulatory surge of LH is the primary event responsible for the induction of maturation of the oocyte, LH and its surrogate human chorionic gonadotropin (hCG) do not act directly on the oocyte due to the absence of functional LH receptors in germ cells. Instead, actions of LH/hCG are mediated either by paracrine factors secreted by LH-responsive somatic cells (theca and mature granulosa cells) or by the transport of cellular messengers from granulosa/cumulus cells to oocytes through intercellular gap junctions [1]. In addition to nuclear maturation exemplified by GVBD and extrusion of the first polar body to complete the first meiotic division, oocytes also undergo cytoplasmic maturation characterized by cytoplasmic changes essential for monospermic fertilization, processing of the sperm, and preparation for development to preimplantation embryos [2, 3]. Although the spermatozoon provides an essential element for embryo generation, the developmental fate of the embryo is principally dictated by the oocyte. However, few studies have explored ovarian factors that may be important for the conditioning of the oocyte in preparation for fertilization and preimplantation development. We used DNA microarray analyses to identify novel ovarian paracrine ligands induced by LH during the preovulatory period (Fig. 1). Immature mice were treated with Humegon (containing follicle stimulating hormone (FSH) and LH activities) and Pregnyl (containing LH/hCG activity) to stimulate follicular maturation and ovulation, respectively. DNA microarray analyses of the ovarian transcriptome during the preovulatory period allowed us to identify the

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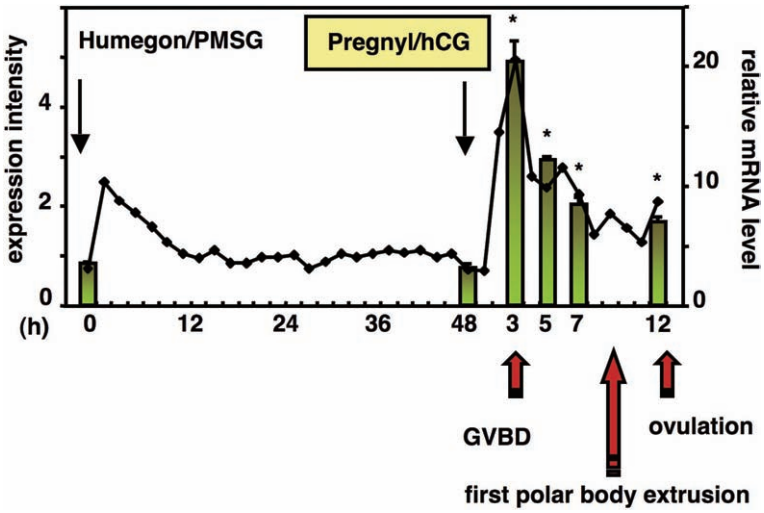

Fig. 1. Identification of LH-stimulated genes by DNA microarray analyses. Immature female B6D2F1 mice were injected with Humegon containing FSH and LH activities to stimulate follicular growth. Forty-eight hours later, some animals were treated with Pregnyl containing LH activity to induce ovulation. Ovaries were dissected from animals sacrificed bi-hourly after Humegon treatment (three mice per group) and hourly after Pregnyl treatment (one mouse per group) for RNA extraction. The pooled follicular phase samples were hybridized to the Affymetrix mouse MGU74v2 arrays A, B, and C. DNA microarray data were confirmed by quantitative real-time RT-PCR of ovarian transcripts in mice treated with pregnant mare serum gonadotropin (PMSG) followed by an ovulatory dose of hCG 48 h later. Line graphs represent DNA microarray data depicting the expression intensity of each transcript (left y axis), whereas bar graphs depict quantitative real-time RT-PCR results (right y axis). Values for expression intensity were derived from the integration of hybridization signals from multiple probe sets for individual genes.

primary candidates of ligand-receptor pairs with major stimulation of their expressions by LH/hCG induction of ovulation. After confirmation of the results of DNA microarray analyses by quantitative real-time RT-PCR, final candidates were obtained by the screening primary candidates based on localization of the ligand-receptor pairs in ovarian follicles. In this review, we introduce insulin like-3 (INSL3), endothelin-1, brain-derived neurotrophic factor (BDNF), and glial cell-line derived neurotrophic factor (GDNF) as novel oocyte maturation factors which were found among the final candidates.

INSL3

INSL3, also know as Leydig insulin-like hormone, was originally named for its exclusive expression in Leydig cells of fetal and adult testes [4]. However, INSL3 is also expressed in thecal and luteal cells of the ovary [5]. Male INSL3 null mice exhibit bilateral cryptorchidism [6, 7], whereas female INSL3 null mice show impaired fertility [6]. Previous studies indicated that testis INSL3 acts as an endocrine factor to activate a G protein coupled receptor, LGR8 (leucine-rich repeat-containing G protein-coupled receptor 8), in the gubernaculum with increases in cAMP production [8]. In mouse ovaries, we found that LH stimulates INSL3 transcripts in theca cells. INSL3, in turn, binds a G protein-coupled receptor, LGR8, expressed in oocytes to activate the inhibitory G (Gi) protein, thus leading to decreases in cAMP production. Treatment with INSL3 initiates meiotic progression of arrested oocytes in preovulatory follicles *in vitro* and *in vivo,* thus demonstrating the importance of the INSL3-LGR8 paracrine system in mediating gonadotropin actions on the resumption of meiosis in oocytes [9].

The prolonged arrest of oocytes in the meiotic prophase (G2/M transition) and subsequent resumption of meiosis is correlated with changes in cAMP levels in the oocyte. Meiotic arrest of the oocyte is most likely maintained by cAMP generated by oocyte adenylyl cyclase, which is controlled by the constitutive action of GPR3 and GPR12 via stimulatory G (Gs) protein [10,

11]. Although LH stimulates cAMP production in follicular somatic cells, a decrease in the intra-oocyte cAMP level is required for meiotic resumption [12]. Indeed, meiotic arrest is released after injection of an antibody for the Gs protein [13]. Although the resumption of meiosis is induced by INSL3 in mammals and by progesterone and insulin in amphibians, a decrease in the intra-oocyte cAMP level is an evolutionarily conserved mechanism for regulating meiotic progression [14]. Our findings of transient stimulation of INSL3 expression in theca cells by LH/hCG, INSL3 suppression of intra-oocyte cAMP levels, and INSL3 induction of oocyte maturation suggest a paracrine role of the INSL3-LGR8 system in mediating preovulatory LH actions [9]. The ovulatory process consists of oocyte maturation, follicle rupture, and luteinization. Earlier studies indicated that cycling rats treated with inhibitors for the oocyte-specific phosphodiesterase 3 enzyme maintained normal cycling and follicle rupture, but ovulated oocytes were immature and not fertilizable [15]. Our study further confirmed the possibility of separating oocyte maturation and follicle rupture, thus providing a basis for fertility regulation with LGR8 modulators.

Endothelin-1

Endothelin-1 is a 21-amino acid multifunctional peptide. In addition to its potent vasoconstrictor actions [16], endothelin-1 is also important in renal, pulmonary, and reproductive physiology [16–22]. In mouse ovaries, we found increases in transcripts of endothelin-1 and endothelin receptor type A (EDNRA) in response to preovulatory LH/hCG stimulation. Immunohistochemical analyses demonstrated localization of EDNRA in granulosa and cumulus cells. In cultured preovulatory follicles, treatment with endothelin-1 promoted oocyte GVBD. The stimulatory effect of endothelin-1 was blocked by cotreatment with antagonists for the type A, but not the related type B, receptor. The stimulatory effect of hCG on GVBD was partially blocked by the same antagonist. The endothelin-1 promotion of GVBD was found to be mediated by the MAPK/ERK pathway but not by the Gi protein. Studies using cumulus—oocyte complexes and denuded oocytes demonstrated that the endothelin-1 actions were mediated by cumulus cells. Furthermore, intrabursal administration with endothelin-1 induced oocyte GVBD in preovulatory follicles. Our findings demonstrated a paracrine role of endothelin-1 in the induction of the resumption of meiosis [23].

Endothelin-1 belongs to a structurally homologous peptide family that includes endothelin-2 and endothelin-3. Endothelin peptides bind to two G protein-coupled receptors, EDNRA and EDNRB. The EDNRA receptor has a high specificity for endothelin-1 (endothelin-1>endothelin-2>endothelin-3), whereas EDNRB binds all three ligands with similar affinity [24, 25]. Our findings indicated the essential role of EDNRA, but not EDNRB, in mediating endothelin-1 [23]. The importance of the endothelin-1/EDNRA signaling system in meiosis resumption could not be investigated in endothelin-1 or EDNRA null mice, because these animals die shortly after birth [26, 27]. It is interesting to note that increases in endothelin-1 transcripts and proteins were evident within 2 h after hCG treatment [28], before the induction of GVBD that was usually found at 4–5 h after hCG treatment *in vivo*. In contrast, a major increase in endothelin-2 levels was found only at 12 h after hCG treatment in the preovulatory rat ovary and endothelin-2 has been found as a paracrine factor important for follicle rupture by disrupting the somatic cell organization, which takes place at 12–14 h after hCG administration [29]. Because endothelin-1 induces meiotic resumption through EDNRA and endothelin-2 regulates follicle rupture by acting through EDNRB [30], it is apparent that the two endothelin peptides regulate different ovulation-related processes in a receptor-, time- and cell type-specific manner.

Endothelin-1, like EGF-like ligands [31], acts through cumulus cells to regulate oocyte maturation [23], whereas INSL3 directly suppresses intra-oocyte cAMP levels [9]. The cellular mechanisms underlying cumulus-oocyte communication during meiotic resumption are only partially known. It is possible that, after the LH surge, the inhibitory influence of the follicular environment is decreased. This could occur as a consequence of a breakdown in gap junction communication between cumulus cells and oocytes [1], leading to the interruption of the transfer of inhibitory molecules (such as cAMP) to the oocyte. However, a role for positive stimuli has also been suggested [9, 31]. It is becoming clear that a combination of both inhibitory and stimulatory factors plays redundant roles to insure the prolonged meiotic arrest before ovulation and the successful oocyte maturation during the ovulatory process induced by the LH surge. Unlike INSL3 [9], endothelin-1 stimulation of oocyte GVBD is not mediated by Gi proteins in oocytes. Accumulating evidences indicate that activation of MAPK in cumulus cells, but not oocytes, is important for gonadotropin-induced meiotic resumption in mammals [32, 33]. We

found the involvement of the MAPK pathway in the endothelin-1 mediation of oocyte maturation [23]. Future studies are required to determine the exact mechanisms underlying endothelin-1 induced GVBD.

BDNF

BDNF is a member of the neurotrophin family of proteins known to activate the high affinity tyrosine kinase (Trk)B receptor and the pan-neurotrophin low-affinity receptor p75 (p75 NTR) [35]. After BDNF binding, TrkB receptor signaling activates multiple signaling pathways, including phosphatidylinositol 3-kinase (PI3K), MAPK/ERK, phospholipase C-γ, and protein kinase C cascades, and plays important roles in cell proliferation, differentiation, and survival in different cell types [35, 36]. Although neurotrophins are widely expressed in the central nervous system and are important for neuronal survival and differentiation [37], they also play important roles in nonneuronal tissues [38]. In the ovary, BDNF was found to be essential for the development of early follicles [39, 40]. Four of the five known neurotrophins, including nerve growth factor (NGF), BDNF, neurotrophin-3, and neurotrophin-4/5 (NT-4/5), and their receptors (TrkA, TrkB, TrkC, and p75 NTR) are expressed in early ovarian follicles [41]. Mice defective in the expression of TrkB or its ligands (BDNF and NT-4/5) exhibit arrest in follicle development at the primary follicle stage [39, 40]. Furthermore, treatment with the Trk receptor inhibitor, K252a, or the combined addition of antibodies against BDNF and NT-4/5 decreased primordial follicle survival *in vitro* [40]. The expression of TrkA and its ligand, NGF, are increased in the theca cells of preovulatory follicles and immunoneutralization of NGF actions inhibit follicle rupture [42, 43]. During the preovulatory period, we demonstrated the increases of BDNF in ovarian granulosa and cumulus cells after LH/hCG stimulation and the exclusive expression of its receptor, TrkB, in oocytes in mice. Ovarian BDNF acts on TrkB receptors expressed exclusively in oocytes to enhance first polar body extrusion of oocytes and to promote the *in vitro* development of zygotes into preimplantation embryos. Furthermore, *in vivo* treatment of mice with a Trk receptor inhibitor suppressed first polar body extrusion and the progression of zygotes to blastocysts. Our *in vitro* and *in vivo* findings demonstrate the essential role of the ovarian paracrine factor, BDNF, in promoting first polar body extrusion and in conditioning the oocytes for optimal fertilization and development into preimplantation embryos [44].

Completion of nuclear maturation involves GVBD and extrusion of the first polar body. Although treatment of cultured COCs with BDNF did not affect GVBD, it facilitated first polar body extrusion in both the mouse and human [44, 45]. Because *in vivo* treatment of animals with the Trk inhibitor also did not affect GVBD of ovulated oocytes in these animals [44], it is apparent that the sequential steps of nuclear maturation of the oocyte are controlled by different paracrine factors. Some oocytes competent to complete nuclear maturation are unable to develop to the blastocyst stage, which is indicative of deficient or defective cytoplasmic maturation of the oocyte [2]. During maturation of preovulatory oocytes, cytoplasmic changes in oocytes are necessary to allow for the acquisition of the maternal components required for optimal development of fertilized oocytes into preimplantation embryos. We demonstrated that *in vitro* treatment of COCs with BDNF not only augmented first polar body extrusion but also enhanced the subsequent development of MII oocytes to two-cell and blastocyst embryos [44]. Furthermore, *in vivo* treatment with the Trk receptor inhibitor indicated the essential role of preovulatory increases of endogenous BDNF in the cytoplasmic maturation of the oocyte, thereby showing a major suppression of embryos capable of developing to the blastocyst stage [44]. Even for embryos developed to the blastocyst stage, pretreatment with the Trk receptor inhibitor decreased their cell numbers by half. Furthermore, oocytes that spontaneously reached the first polar body stage had lower levels of glutathione, which is believed to be important in the fertilization of MII oocytes by facilitating sperm nuclear decondensing activity [46]. Because BDNF treatment enhanced oocyte glutathione content [44], these findings suggest that BDNF could play a role in successful fertilization. Thus, ovarian BDNF could activate separate downstream pathways in the oocyte to facilitate nuclear maturation as well as cytoplasmic maturation.

GDNF

GDNF was first identified as a survival factor for several types of neurons [47, 48]. GDNF acts through a two component receptor system consisting of the ligand-specific binding subunit, GDNF family receptor-alpha1 (GFRA1) and the common signal transduction subunit, ret proto-oncogene (Ret) [49]. Although GDNF and its receptor system are expressed in the nervous system, their expression has also been detected in several peripheral tissues, including the ovary and testis

[50]. In the testis, GDNF contributes to paracrine regulation of spermatogonial self-renewal and differentiation [51] and acts as the primary growth factor supporting self-renewal of spermatogonial stem cells in mice [52]. We demonstrated the preovulatory increases of GDNF transcripts and proteins in ovarian cumulus, granulosa, and theca cells after LH/hCG stimulation, and the expression of its receptors, GFRA1 and Ret, in mouse oocytes. Treatment of cumulus—oocyte complexes with GDNF enhanced first polar body extrusion with an increase in cyclin B1 synthesis and the GDNF actions are likely mediated by its receptor, GFRA1, and a co-receptor, Ret, both expressed in oocytes. However, treatment with GDNF did not affect GVBD and the competence of oocytes to complete preimplantation development. Our study demonstrates the important role of an ovarian paracrine factor, GDNF, in the promotion of completion of meiosis I [28].

Both BDNF and GDNF are capable of promoting first polar body extrusion, but not GVBD, and have redundant roles in first polar body extrusion [28, 44]. Mouse oocytes do not require *de novo* synthesis of proteins to undergo GVBD *in vitro*, whereas the synthesis of cyclin B1 is indispensable for the progression of meiotic maturation after GVBD [53, 54]. Thus, our data on the increase in cyclin B1 protein in MI oocytes following GDNF treatment suggest its contribution to the GDNF promotion of completion of meiosis I [28]. Although both cumulus cells and oocytes express GFRA1 and Ret receptors, GDNF induced first polar body extrusion in denuded oocytes, suggesting its direct effect on oocytes. In contrast to BDNF [44], ovarian GDNF showed no effect on the cytoplasmic maturation of preovulatory oocytes [28]. A previous study reported that the proportion of parthenogenetically activated porcine oocytes forming blastocysts was increased after *in vitro* culture with GDNF [55]. In contrast to our serum-free experimental setting for oocyte maturation, LH, FSH, EGF, and 10% porcine follicular fluid were included in the maturation medium of that study. Thus, GDNF may require additional hormonal factors and/or unknown factors present in the follicular fluid for the optimal induction of the cytoplasmic maturation of oocytes. However, the low levels of BDNF did not augment GDNF-stimulated cytoplasmic maturation [28].

Because mutant mice with defects in GDNF, GFRA1, or Ret show similar phenotypes and died on the first postnatal day [56–59], no female mice were available for investigating changes in ovarian functions. Furthermore, GDNF preferentially interacts with the receptor complex GFRA1-Ret, but it can also activate the GFRA2-Ret complex. Although GFRA1 binds GDNF with high affinity, it also interacts with other GDNF family members including neurturin and artemin [49]. Therefore, studies on the role of GDNF during oocyte maturation in pups lacking GFRA1 are complicated due to the overlapping actions of different GDNF family members and their receptor complexes.

Conclusion

The important roles of ovarian paracrine factors in the regulation of oocyte functions are becoming clear. Genome-wide analyses based on our DNA microarray datasets indicated that a limited number of ligands are induced by the preovulatory LH surge to promote oocyte maturation. It is becoming apparent that redundant intra-ovarian pathways in oocytes and cumulus cells are activated during the preovulatory period to ensure successful oocyte maturation, fertilization, and early embryo development. Gene expression during oocyte maturation, fertilization, and early embryo development is regulated mainly by translational activation of maternally derived mRNAs, and the proper conditioning of the oocyte cytoplasm enables the development of totipotent blastocysts. Elucidation of the potentially overlaying mechanisms underlying these ovarian paracrine signaling systems would provide better strategies for *in vitro* maturation of oocytes and its clinical application in assisted reproductive technology, and allow the formulation of new contraceptive strategies.

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