REVIEW ARTICLE

Role of oocyte-derived paracrine factors in follicular development

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ABSTRACT

Mammalian oocytes secrete transforming growth factor \( \beta \) (TGF-\( \beta \)) superfamily proteins, such as growth differentiation factor 9 (GDF9), bone morphogenetic protein 6 (BMP6) and BMP15, and fibroblast growth factors (FGFs). These oocyte-derived paracrine factors (ODPFs) play essential roles in regulating the differentiation and function of somatic granulosa cells as well as the development of ovarian follicles. In addition to the importance of individual ODPFs, emerging evidence suggests that the interaction of ODPF signals with other intra-follicular signals, such as estrogen, is critical for folliculogenesis. In this review, we will discuss the current understanding of the role of ODPFs in follicular development with an emphasis on their interaction with estrogen signaling in regulation of the differentiation and function of granulosa cells.

Key words: cumulus cell, estrogen, follicle, granulosa cell, oocyte.

INTRODUCTION

Although many intra- and extra-ovarian factors, including follicle stimulating hormone (FSH), luteinizing hormone (LH) and estrogen, play important roles in the development of follicles, paracrine signals derived from oocytes seem to be one of the predominant determinants of the developmental state of follicles. This was evidenced, for example, by a study of follicles in which the developmental stages of oocytes and follicular somatic cells were mismatched (Eppig et al. 2002). In that study, when growing oocytes from 12-day-old mice were combined with the somatic cells from neonatal ovaries, the developmental stage of the follicles caught up to that of oocytes rather than that of somatic cells. Therefore, oocytes play a critical role in determining the fate of ovarian somatic granulosa cells and ultimately the rate of development of follicles.

The mechanism by which oocytes coordinate the development of follicles has been studied actively for decades, and the emerging evidence suggests that cooperation of the oocyte-derive paracrine signal with other intra-follicular signals, such as estrogen signals, is critical for the development and function of follicles. This mini-review will focus on the current state of our understanding of the regulation of follicular development by oocyte-derived paracrine factors (ODPFs) with an emphasis on their interaction with other intra-follicular signals.

OVERVIEW OF FOLLICULAR DEVELOPMENT

Ovarian follicular development starts from the generation of primordial follicles in which squamous somatic cells, often called pre-granulosa cells, encircle a primary oocyte arrested at the first meiotic prophase (Fig. 1). An oocyte-specific transcription factor, folliculogenesis specific basic helix-loop-helix (FIGLA), is required for the formation of primordial follicles, since the ovaries of Figla-deficient mice have no primordial follicles (Soyal et al. 2000). Therefore, oocytes are required from the very beginning of the follicular development.

When primordial follicles develop into primary follicles, the oocytes begin to grow and the shape of the granulosa cells becomes cuboidal. Then, as the granulosa cells proliferate, two or more layers of...
granulosa cells encircle the oocytes and the follicles become covered with theca cells. At this stage, the follicles are called secondary follicles. Female mice deficient in growth differentiation factor 9 (GDF9, see below), one of the ODPFs, are infertile due to a block of folliculogenesis at the primary stage, indicating that oocyte-produced GDF9 is required for the transition of primary to secondary follicles (Dong et al. 1996). Interestingly, the expression levels of transcripts encoding inhibin alpha (Inha) are significantly up-regulated in the Gdf9-deficient ovaries (Elvin et al. 1999), and the block of folliculogenesis at the primary stage was not observed in Gdf9/Inha double knockout mice (Wu et al. 2004). This suggests that aberrant expression of Inha is the main cause of the block of follicular development observed in Gdf9-deficient ovaries.

When a secondary follicle develops and becomes a tertiary follicle, a fluid-filled antrum is formed between the granulosa cell layers. The follicles before and after antrum formation are called pre-antral and antral follicles, respectively. The transition of pre-antral to antral follicles is accompanied by the differentiation of granulosa cells of pre-antral follicles (pre-antral granulosa cells) to cumulus cells, which encircle oocytes and play an essential role in oocyte development, and mural granulosa cells, which line the follicular wall and serve a primary endocrine function (Fig. 1). The opposing gradients of extra-follicular FSH and intra-follicular ODPF signals are critical for determining the fate of the granulosa cell differentiation (Diaz et al. 2007a). Whereas FSH signal promotes pre-antral granulosa cells to differentiate into mural granulosa cells, ODPFs promote cumulus cell differentiation. In the following section, the requirement of ODPFs in determining granulosa cell differentiation as well as follicular development during the transition of pre-antral to antral follicles is reviewed.

**OOCYTE-DERIVED PARACRINE FACTORS (ODPFs)**

Transforming growth factor β (TGF-β) superfamily proteins are the most characterized ODPFs. Mammalian oocytes secrete several ligands of the TGF-β superfamily, including GDF9 and bone morphogenetic proteins (BMPs) such as BMP15 and BMP6. The expression of proteins or transcripts encoding these ligands is detected in oocytes of many mammalian species, including mice (Lyons et al. 1989; McGrath et al. 1995; Dong et al. 1996; Dube et al. 1998; Elvin et al. 2000), rats (Hayashi et al. 1999; Jaatinen et al. 1999; Erickson & Shimasaki 2003), cattle (Bodensteiner et al. 1999), sheep (Bodensteiner et al. 1999; Galloway et al. 2000), goats (Silva et al. 2005), pigs (Prochazka et al. 2004; Brankin et al. 2005), rhesus monkeys (Duffy 2003) and humans (Sidis et al. 1998; Aaltonen et al. 1999). In some species, including primates, goats and pigs, the expression of these ligands is also detected in granulosa cells (Sidis et al. 1998; Duffy 2003; Prochazka et al. 2004; Brankin et al. 2005; Silva et al. 2005).

The critical roles of these TGF-β superfamily members in normal follicular development and female fertility have mainly been revealed through the investigation of animals that are deficient in these proteins. For example, ewes which have a homozygous mutation in the BMP15 gene are infertile due to the abnormal development of follicles after the primary stage (Galloway et al. 2000). Similar infertile phenotypes have been reported in ewes with many other natural mutations of GDF9 or BMP15 genes (Hanrahan et al. 2004; Bodin et al. 2007; Martinez-Royo et al. 2008; Monteagudo et al. 2009). Injecting a GDF9 gene fragment into the ovaries of prepubertal gilts results in an increase in the numbers of primary follicles, whereas it induces a decrease in the number of primordial follicles (Shimizu et al. 2004). In addition, abnormal follicular development with impaired fertility has been reported in sheep and cattle actively immunized against BMP15 and GDF9 (Juengel et al. 2002, 2009). Therefore, GDF9 and BMP15 play a critical role in regulating follicular development in these mammalian species.

In contrast, female mice with homozygous mutation in Bmp15 and/or Bmp6 do not exhibit an aberrant phenotype in their ovaries (Yan et al. 2001; Sugiura et al. 2002, 2009).
Synergistic effects of GDF9 and BMP15 on granulosa cell development and function, as well as on follicular development, were first reported in mice. Bmp15 null mice exhibit a relatively mild phenotype, whereas additional deletion of one allele of the Gdf9 gene (i.e., Bmp15+/−/Gdf9−/− mice) results in severe infertility (Yan et al. 2001; Su et al. 2004). A similar genetic interaction between BMP15 and GDF9 genes was also reported in sheep (Hanrahan et al. 2004). At the protein level, many studies have shown the existence of this synergism using recombinant proteins (McNatty et al. 2005a,b; Mottershead et al. 2011). Although the mechanisms underlying the synergistic interaction of BMP15 and GDF9 signaling are not fully resolved, a recent study has suggested involvement of the BMP15/GDF9 heterodimer in this interaction (Peng et al. 2013a). This study showed that the BMP15/GDF9 heterodimer is 10- to 3000-fold more biopotent than the homodimers of BMP15 or GDF9. The other well-known factors derived from oocytes are fibroblast growth factors (FGFs). The production of FGFs by oocytes has long been recognized in mice (Valve et al. 1997) and cattle (Buratinin et al. 2005a, b, 2007). However, the function of FGF8 during follicular development was not understood until more recently, when FGF8 and BMP15 were shown to promote the expression of genes encoding glycolytic enzymes in mouse cumulus cells in vitro (Sugiura et al. 2005, 2007). In addition, FGF8 promoted the suppressive effect of recombinant BMPs on FSH-induced cyclic adenosine monophosphate (cAMP) production and the BMP-stimulated SMAD1/5/8 phosphorylation in diethylstilbestrol-primed rat preantral granulosa cells (Miyoshi et al. 2010). Therefore, a cooperative interaction between FGF and BMP signals may be critical in the regulation of granulosa cell development and function. However, since human recombinant mouse proteins were used in these studies, the question of whether endogenous mouse/rat BMPs undergo the same interaction with FGFs may require further investigation. Importantly, the mouse BMP15 homodimer appears to exhibit less activity than the human BMP15 homodimer (Peng et al. 2013a).

CROSSTALK BETWEEN THE ODPF SIGNAL AND THE OTHER INTRAFOLLICULAR SIGNALS

Although paracrine signals derived from oocytes seem to be one of the predominant determinants of granulosa cell differentiation, other follicular signals, such as FSH, LH and steroids, are also important. Obviously these follicular signals affect each other, and the interaction between these signals is critical for the proper regulation of granulosa cell development. Recent studies revealed the importance of the interaction between oocyte-derived paracrine signals and estrogen signals for regulation of the development and function of granulosa cells. The following section summarizes the current state of our understanding of the interaction between signals of ODPFs and estrogen.

Estrogen signals within the follicles are mainly mediated by estrogen receptor 2 (ESR2; also known as estrogen receptor β). Est2-deficient mice are subfertile because of their attenuated follicular development (Krege et al. 1998; Cheng et al. 2002; Emmen et al. 2005) and reduced ovulation rate (Couse et al. 2005). Moreover, estrogen promotes proliferation (Rao et al. 1978), suppresses apoptosis of granulosa cells (Billig et al. 1993) and augments the effects of FSH on granulosa cell differentiation and function (Adashi & Hsueh 1982; Zhuang et al. 1982). Therefore, estrogen itself plays important roles in regulating the development and function of granulosa cells as well as the development of follicles.

The cooperative action of ODPFs and estrogen was first reported in a study using rat primary cultured granulosa cells (Otsuka et al. 2005). In the presence of oocytes, estrogen promoted the FSH-stimulated expression of several transcripts, including Cyp19a1, Fshr and Lhcgr, and the production of cAMP by rat granulosa cells; however, in the absence of oocytes, estrogen had no effect. Therefore, ODPFs are required for the action of estrogen on FSH signaling in rat granulosa cells.

Cumulus expansion or mucification is an essential process for normal ovulation (Chen et al. 1993). Normal expansion requires the expression of several transcripts encoding HAS2, PTGS2, PTX3 and TNFAIP6 (Davies et al. 1999; Varani et al. 2002; Fulop et al. 2003; Ochsner et al. 2003; Sugiura et al. 2009). Cumulus expansion is induced by an LH surge the signal of which within the follicles is mediated by epidermal growth factor (EGF)-like peptides produced by granulosa cells (Park et al. 2004; Shimada et al. 2006). Cumulus cells of Bmp15 null or Bmp15+/−/Gdf9−/− mice are less able to undergo expansion and to express Has2 and Ptgs2 transcripts (Yan et al. 2001; Su et al. 2004) and ODPFs are required for preantral granulosa cells to acquire the ability to undergo expansion in vitro (Diaz et al. 2007b). Therefore, oocyte-produced GDF9 and
BMP15 are required for cumulus cells to become competent to undergo expansion. In addition to the ODPFs, estrogen appears to be critical for the cumulus cells to become competent to undergo the expansion process, since the cumulus cells of estrogen-deficient mice are not competent for full expansion and expression of the PtgS2 transcript (Dupont et al. 2000; Couse et al. 2005; Emmen et al. 2005). Our recent study also showed that the cooperative interaction of estrogen and ODPFs, especially BMP15 and GDF9, is required for maintaining cumulus cell-competence to undergo the expansion process (Sugiura et al. 2010b). Therefore, both ODPFs and estrogen are required for the cumulus cells to become competent and to maintain their competence.

Another example of the ODPF/estrogen interaction was recently reported in the context of regulation of the meiotic arrest of oocytes in Graafian follicles. Natriuretic peptide type C (NPPC) (also known as C-type natriuretic peptide, CNP) is expressed by mural granulosa cells, whereas its receptor, natriuretic peptide receptor 2 (NPR2), is mainly expressed by cumulus cells (Zhang et al. 2010). The expression of Npr2 in cumulus cells is cooperatively controlled by signals of ODPFs and estrogen (Zhang et al. 2010, 2011; Lee et al. 2013). Treating cumulus-oocyte complexes (COCs) with NPPC was shown to prevent the meiotic resumption of mouse oocytes in vitro. Moreover, mutant mice for Nppc or Npr2 exhibited precocious resumption of oocyte meiosis in Graafian follicles (Zhang et al. 2010; Kiyosu et al. 2012; Tsuji et al. 2012). The importance of the NPPC/NPR2 system for the meiotic arrest of oocytes has also been demonstrated in other mammalian species, including goats (Peng et al. 2013b), pigs (Hiradate et al. 2013) and humans (Kawamura et al. 2011). Therefore, the NPPC/NPR2 system appears to be a common mechanism for maintenance of oocyte meiotic arrest in mammals.

To understand the underlying mechanism of the ODPF/estrogen signal cooperation in more detail, we recently conducted microarray comparisons in which the effects of ODPFs and estrogen on the cumulus cell transcriptome were examined (Emori et al. 2013). For this purpose, we cultured isolated cumulus cell complexes (oocytectomized (OOX) cumulus cells) with or without the presence of ODPFs and/or estrogen. Then, the transcriptomes of the cumulus cells were analyzed with microarray analyses. The biological processes regulated by ODPFs in cumulus cells are largely unaffected by the presence of estrogen, whereas those regulated by estrogen are significantly affected by ODPFs. For example, in the presence of ODPFs, estrogen significantly promoted cumulus cell biological processes related to phosphorylation-mediated signal transduction, including the signaling pathways of EGF, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). The signaling pathways of EGF (Park et al. 2004), VEGF (Shimizu et al. 2003) and PDGF (May et al. 1992; Duleba et al. 1999; Nilsson et al. 2006; Sleer & Taylor 2007; Schmahl et al. 2008) have been implicated as critical regulators of follicular development. Therefore, the cooperative interaction between ODPFs and estrogen is critical for regulating follicular development.

The underlying mechanism governing the cooperative interaction of ODPFs and estrogen is yet to be determined. Generally, signals of estrogen are affected by multiple co-factors which bind with receptors of estrogen (McKenna et al. 1999). We previously reported that the expression of one of the ESR-binding proteins, nuclear receptor interacting protein 1 (Nrip1, also known as RIP140), in cumulus cells is regulated by ODPFs (Sugiura et al. 2010b). In addition, the expressions of several ESR-binding proteins, including Foxl2 and Noa3, in cumulus cells are regulated by ODPFs (Emori et al. 2013; unpublished data). Therefore, regulation of the expression of these ESR co-factors by ODPFs may be the critical mechanism in the cooperative interaction of ODPFs and estrogen.

Conclusion

Many extra- and intra-follicular factors, including gonadotropins, steroids and growth factors produced within follicles, have been identified as essential components of a signal network that governs follicular development. The signals of these factors affect each other, and the coordination of these signals is critical for production of functional oocytes. Accumulating evidences suggests that the ODPF signal, interacting with other follicular signals, plays an active role in determining the state of differentiation and function of granulosa cells as well as the development of follicles. Ongoing research into the signal interactions will provide a new perspective on our understanding of follicular development.

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