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Paracrine and autocrine factors in the differentiation of the cumulus-oocyte complex

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Abstract

A better understanding of the paracrine and autocrine regulatory loops within the cumulus-oocyte complex (COC) is fundamental for the improvement of *in vitro* maturation (IVM) outcomes in humans and domestic species. This review presents the most important local regulators identified in the COC to date with special attention to those secreted by the oocyte and acting on cumulus cells, as well as their roles in different processes crucial for the successful maturation of the COC. An autocrine regulatory loop mediated by epidermal growth factor-like (EGF-like) peptides in cumulus cells triggers COC maturation. During COC differentiation, oocyte secreted factors (OSFs), particularly members of the transforming growth factor-β (TGFβ) and fibroblast growth factor (FGF) families, regulate meiotic resumption, cumulus expansion, cumulus metabolism, apoptosis and steroidogenesis.

Keywords: cumulus-oocyte complex, EGF-like factors, FGF, oocyte secreted factors, TGFβ.

Introduction

A very small fraction of the follicles assembled during ovarian development reaches ovulation and the great majority of the oocytes available are not fertilized under physiological conditions in domestic species. The female reproductive potential can be explored by assisted reproductive technologies (ART) such as *in vitro* maturation (IVM) of cumulus-oocyte complexes (COC) followed by *in vitro* fertilization (IVF) and embryo transfer. However, it is well known that IVM compromises oocyte developmental competence (Rizos *et al*., 2002). Therefore, a deeper knowledge of the mechanisms regulating COC differentiation is needed so the culture system can be adjusted to mimic more closely the physiological conditions allowing better IVM/IVF outcomes.

During the last two decades, a robust body of data has evidenced that maturation of the COC is locally regulated after the ovulatory gonadotropin stimulus. In addition, an autocrine regulatory loop within cumulus cells and a bidirectional paracrine communication between the oocyte and cumulus cells have been demonstrated to be essential for fertility (Conti *et al*., 2006; Gilchrist *et al*., 2008). The purpose of this review is to highlight some of these main autocrine and paracrine factors and their roles in the control of different aspects of COC postovulatory differentiation such as cumulus expansion, apoptosis, energetic metabolism, meiosis progression and steroidogenesis.

In vivo and *in vitro* maturation of the cumulus-oocyte complex

The ovulatory LH peak triggers the maturation of the COC via mural granulosa cells since neither the oocyte nor cumulus cells express the LH receptor in physiologically relevant levels (Peng *et al*., 1991; van Tol *et al*., 1996; Richards *et al*., 2002). In response to LH, murine mural granulosa cells secrete epidermal growth factor (EGF)-like family members, amphiregulin (AREG), epiregulin (EREG) and betacellulin (BTC), which act upon cumulus cells, where they stimulate their own synthesis (Park *et al*., 2004; Ashkenazi *et al*., 2005; Conti *et al*., 2006). A similar but not identical mediation appears to occur in domestic species as expression of AREG and EREG, but not of BTC, was upregulated by gonadotropins in cumulus cells from cows and pigs (Procházka *et al*., 2011, Caixeta, 2012). EGF-like factors also appear to mediate the effects of FSH on cumulus cells in the absence of mural cells and LH stimulation during IVM. This was evidenced by the increase in AREG and EREG expression in porcine and bovine cumulus cells cultured with increasing doses of FSH (Procházka *et al*., 2011, Caixeta, 2012).

EGF-like factors are originally produced as transmembrane precursors that must be cleaved by members of the disintegrin and metalloproteinase (ADAM) family to allow the release of soluble molecules capable of activating the EGF receptor (EGFR) in cumulus cells (Ben-Ami *et al*., 2006). Subsequently, EGFR signaling through ERK1/2 [extracellular signal regulated kinases 1 and 2, also known as mitogen-activated protein kinases 3 and 1 (MAPK3/1)], stimulates oocyte maturation and the production of several proteins required for cumulus expansion, such as hyaluronan synthase 2 (HAS2), prostaglandin-endoperoxide synthase 2 (PTGS2), tumor necrosis factor-stimulated gene 6 protein (TSG6) and pentraxin 3 (PTX3; Ashkenazi *et al*., 2005; Conti *et al*., 2006; Shimada *et al*., 2006; Fan *et al*., 2009).

Meiosis resumption

The disruption of EGFR signaling prevents meiosis resumption in mice, indicating that granulosa cell-derived EGF-like factors trigger oocyte nuclear

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maturation (Downs and Chen, 2008). Although the mechanisms following EGFR activation and ERK1/2 phosphorylation are not completely known, they appear to involve the phosphorylation of conexin 43 (Cx43), which causes gap junctions closure and, consequently, the interruption of cAMP and cGMP influx from cumulus cells into the oocyte. These second messengers play pivotal roles in meiosis regulation; while cAMP suppresses the activity of maturation promoting factor (MPF), cGMP inhibits the activity of type 3 phosphodiesterase (PDE3), the enzyme that degrades cAMP in the oocyte. Therefore, the interruption of cGMP influx causes a further and dramatic decrease in cAMP levels in the oocyte, allowing activation of maturation promoting factor (MPF), and thus meiosis resumption (reviewed by Gilchrist, 2011).

Recent studies have demonstrated that cGMP availability in the oocyte is also regulated at the production level in cumulus cells by paracrine factors. In mice, mural granulosa cells express natriuretic peptide precursor type C (NPPC), while cumulus cells surrounding the oocyte express the NPPC receptor, *NPR2*. Treatment with NPPC increased levels of cGMP in cumulus cells and oocytes and inhibited meiotic resumption in mice. Conversely, meiosis resumption was triggered precociously in NPPc or NPR2 mutant mice. The increase in cGMP levels induced by NPPC in oocytes likely results from transfer of cGMP from cumulus cells as oocytes do not express NPR2. Nevertheless, the oocyte is not a passive agent in this process as oocyte derived bone morphogenetic protein 15 (BMP15), growth-differentiation factor 9 (GDF9) and fibroblast growth factor 8 (FGF8) synergistically stimulate the expression of NPR2 in cumulus cells of mice (Zhang *et al*., 2010b). Interestingly, these data explain, at least in part, how the follicular environment maintains meiotic arrest before the LH surge. The detection of FGF8, BMP15 and GFD9 mRNAs in oocytes from domestic mammals suggest that this regulatory mechanism is preserved across different species (Buratini *et al*., 2005; Crawford and McNatty, 2012).

Fibroblast growth factor 10 (FGF10) and kit ligand (KL) also appear to regulate oocyte nuclear maturation in a paracrine manner. FGF10 is expressed by the oocyte, activates FGF receptors in cumulus cells and oocytes, and increases the proportion of oocytes extruding the first polar body when added to the IVM medium in cattle (Berisha *et al*., 2004; Buratini *et al*., 2007; Zhang *et al*., 2010a). However, when added to a co-culture system containing follicular hemisections that prevents meiosis progression, FGF10 blocked angiotensin II (Ang II) induced meiotic resumption (Siqueira *et al*., 2012). The same study provided evidence that Ang II, progesterone and prostaglandins are sequential steps in a pathway leading to nuclear maturation. Since FGF10 had been previously shown to inhibit the expression of Ang II receptors (AT2; Portela *et al*., 2008), and members of the FGF10 family to reduce progesterone and estradiol synthesis by granulosa cells (Parrot and Skinner, 1998; Buratini *et al*., 2007), the negative effect of FGF10 on nuclear maturation in this culture system was interpreted as a possible consequence of its inhibitory effects on AT2 expression and steroidogenesis (Siqueira *et al*., 2012).

Kit ligand (KL) is predominantly expressed by mural granulosa cells but is also present in cumulus cells, while its receptor, cKit, is expressed by the oocyte in mice (Ye *et al*., 2009). The importance of KL/cKit signaling for primordial follicle activation has been long recognized (reviewed by Fortune *et al*., 2011), whilst evidence of its involvement in the regulation of late oocyte maturation are more recent and less robust. In mice, KL stimulated first polar body extrusion but did not change embryo development following IVM (Ye *et al*., 2009). KL possibly interacts with oocyte derived BMP15 and GDF9 in the control of COC differentiation as KL expression is stimulated by BMP15 and inhibited by GDF9 in murine preantral follicles (reviewed by Kidder and Vanderhyden, 2010).

Cumulus expansion

Cumulus expansion is also triggered by EGF-like factors, which then stimulate the expression of several genes crucial for expansion such as prostaglandin-endoperoxide synthase 2 (PTGS2), also known as cyclooxygenase 2 (COX2), hyaluronan synthase 2 (HAS2), tumor necrosis factor alpha-induced protein 6 (TSG6) and pentraxin 3 (PTX3; Park *et al*., 2004; Ashkenazi *et al*., 2005; Shimada *et al*., 2006). Hyaluronan synthase 2 (HAS2) is a key enzyme for the synthesis of hyaluronic acid, the main component of the extracellular matrix, from products of the cellular metabolism such as hexosamines, glucosamines and glucose (Chen *et al*., 1990; Schoenfelder and Einspanier, 2003). Prostaglandin-endoperoxide synthase 2 (PTGS2) regulates the production of PGE2, which is absolutely required for ovulation and cumulus expansion (Eppig, 1981; Hizaki *et al*., 1999; Calder *et al*., 2001). Silencing of PTGS2 or disruption of PGE2 signaling decrease TSG6 expression in murine cumulus cells (Ochsner *et al*., 2003; Takahashi *et al*., 2006), which is needed to stabilize hyaluronan in the extracellular matrix of expanded cumulus (Richards, 2005). In fact, TSG6 has affinity for PTX3 and both proteins interact to stabilize the extracellular matrix (Richards, 2005). Mutant mice with suppressed expression of TSG6 or PTX3 display impaired cumulus expansion and are infertile (Varani *et al*., 2002; Fulop *et al*., 2003; Scarchilli *et al*., 2007). Interestingly, HAS2, PTGS2, TSG6 and PTX3 mRNA expression have been positively associated with enhanced embryo development and thus these genes have been suggested as cumulus markers of oocyte developmental competence (Assidi *et al*., 2008; Tesfaye *et al*., 2009).

Oocyte secreted factors (OSFs) are absolutely required for cumulus expansion in mice, whereas expansion can be induced by FSH in oocytectomized COCs from pigs and cows (Vanderhyden *et al*., 1990; Prochazka *et al*., 1991; Ralph *et al*., 1995). Several members of the transforming growth factor β (TGFβ) superfamily such as TGFβ1, TGFβ2, BMP6 and activin are expressed by the oocyte and stimulate cumulus expansion *in vitro* in rodents, but special attention has been given to BMP15 and GDF9 (reviewed by Gilchrist *et al*., 2008). An interesting and recent study compared mRNA abundance of BMP15 and GDF9 in oocytes from different species; GDF9 was predominant in rodents whereas BMP15 was predominant in pigs and monoovular domestic species (Crawford and McNatty, 2012). Although not absolutely required, OSFs seem to regulate cumulus expansion in domestic species as the addition of FGF10 to the IVM medium enhanced expansion in cattle (Zhang *et al*., 2010a). The addition of BMP15 or FGF10 to the IVM medium improved blastocyst rates in cattle (Hussein *et al*., 2006, 2011; Zhang *et al*., 2010a), and thus enhancement of cumulus expansion might be involved in the mechanisms by which these paracrine factors benefit oocyte developmental competence.

Cumulus metabolism

The regulation of cumulus metabolism is critical for COC successful maturation. Cumulus cells uptake glucose, which is utilized to generate energetic compounds to be delivered to the oocyte and substrates for the production of the extracellular matrix (Sutton-McDowall *et al*., 2010). The products of glycolysis, particularly pyruvate, are transferred through gap junctions to the oocyte, which is incapable of oxidizing glucose (Leese and Barton, 1985). In mice, removal of the oocyte from the COC (oocytectomy) decreased the expression and activity of glycolytic enzymes in cumulus cells, which was reversed when oocytectomized COCs were co-cultured with fully grown oocytes, indicating that OSFs mediate these effects (Sugiura *et al*., 2005). In fact, BMP15 and FGF8 were shown to cooperatively stimulate the expression of platelet phosphofructokinase (PFKP) and lactate dehydrogenase A (LDHA), and to promote glycolytic activity in oocytectomized COCs from mice (Sugiura *et al*., 2007). In contrast, the removal of the oocyte from bovine COCs did not alter the metabolic activity of cumulus cells as indicated by production of L-lactate and glucose consumption (Sutton *et al*., 2003). Therefore, it is possible that cumulus derived factors have a more important role in the regulation of glycolysis in larger mammals.

As IVM proceeds, there is an increase in glucose consumption while production of L-lactate remains constant, which reflects an increasing proportion of glucose being utilized by the somatic cell compartment for the secretion of the extracellular matrix and mucification of cumulus cells (Sutton-McDowall *et al*., 2004). The hexosamine biosynthesis pathway leads to the production of the glucosaminoglycans that constitute the extracellular matrix (Sutton-McDowall *et al*., 2010). Since OSFs have been demonstrated to enhance cumulus expansion, their involvement in the regulation of the hexosamine pathway represents an interesting hypothesis still not addressed.

Apoptosis

The microsurgical removal of the oocyte from the COC increased the levels of apoptosis in bovine cumulus cells, which was reversed when denuded oocytes were added to culture. The anti-apoptotic role of OSFs is further suggested by lower incidence of apoptosis in the corona radiata in comparison with cumulus cells from the outer side of the COC. The pro- and anti-apoptotic genes BAX and BCL-2 appear to mediate at least in part the anti-apoptotic action of OSFs as oocytectomy increased the expression of BAX and decreased the expression of BCL-2 in cumulus cells. BMP6 and BMP15 are likely included among the OSFs in charge of suppressing apoptosis in cumulus cells as treatment with both but not with GDF9 protected bovine cumulus cells from apoptosis and modulated BCL-2 and BAX expression accordingly (Hussein *et al*., 2005).

The observation that the MAPK pathway inhibits apoptosis in bovine cumulus cells through the control of FAS, BAX and BIRC4 transcription suggests that oocyte derived FGFs might also be included among the anti-apoptotic OSFs (Paula-Lopes *et al*., 2007). This is in agreement with previously reported anti-apoptotic action of FGFs in other tissues (Upadhyay *et al*., 2005).

Steroidogenesis

The oocyte prevents luteinization of cumulus cells by secreting factors that inhibit the expression of the LH receptor (LHCGR) and of the steroidogenic enzyme P450 side chain cleavage (CYP11A1, Eppig *et al*., 1997; Diaz *et al*., 2007), limiting secretion of progesterone within the murine, porcine and bovine COC (Vanderhyden *et al*., 1993; Coskun *et al*., 1995; Li *et al*., 2000; reviewed by Gilchrist *et al*., 2008). Nevertheless, steroidogenesis still occurs in the COC and appears to be important for its maturation. Whilst OSFs stimulate the production of estradiol in murine cumulus cells, the opposite happens in the cow (Vanderhyden *et al*., 1993; Glister *et al*., 2003). In mice, full cumulus expansion requires estradiol, which acts in concert with GDF9 and BMP15 to promote expansion competence (Sugiura *et al*., 2010).

Progesterone also seems to play an important role in the control of COC differentiation as progesterone receptors (PGR) are expressed by the oocyte and cumulus cells (Aparicio *et al*., 2011). The

steroidogenic enzymes STAR and P450SCC are also present in bovine cumulus cells and their expression increases in accordance with the increasing production of progesterone along IVM (Nuttinck *et al*., 2008). In a recent study in cattle, progesterone induced nuclear maturation *in vitro* and the intrafollicular injection of a PGR antagonist prevented meiotic resumption. Progesterone-induced meiosis resumption was abolished by co-treatment with indomethacin, indicating that progesterone stimulates meiosis progression through the production of prostaglandins (Siqueira *et al*., 2012). Moreover, disruption of progesterone signaling compromised cumulus expansion and embryo development in cattle (Aparicio *et al*., 2011). These results agree with the identification of PGR as a marker of developmental competence in bovine cumulus cells (Assidi *et al*., 2008).

Concluding remarks

The maturation of the COC is triggered by an autocrine loop within cumulus cells, in which EGF-like factors stimulate their own production, cleavage and release. A bidirectional paracrine communication between the oocyte and cumulus cells regulates cumulus expansion, nuclear maturation, apoptosis, glucose metabolism and steroidogenesis in the COC. Members of the TGFβ and FGF families are important oocyte secreted factors that influence several processes relevant to COC maturation. Although the oocyte prevents luteinization of cumulus cells, steroidogenesis still occurs during COC maturation and steroids are important local regulators of oocyte and cumulus cells differentiation. Finally, caution should be taken to extrapolate regulatory mechanisms between different species, particularly between mice and larger mammals, as expression patterns and the relative importance of oocyte secreted factors seem to differ.

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