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Follicular environment and oocyte maturation: roles of local peptides and steroids

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Abstract

A large amount of data on the mechanisms regulating cumulus-oocyte maturation in mammals has been generated in the last 20 years. It has been made clear that oocyte-secreted factors play a central role in the control of cumulus differentiation and oocyte developmental competence. However, more recent data indicate that cumulus-derived factors are also involved. In this mini-review, we have compiled and discussed data produced in our laboratory about the involvement of oocyte and cumulus-derived peptides, including fibroblast growth factors, bone morphogenetic protein 15, Kit ligand and natriuretic peptide C, in the regulation of cumulus metabolism and oocyte nuclear maturation. In addition, we discuss the interaction of follicular steroids with natriuretic peptide C in the control of meiosis progression.

Keywords*:* oocyte, cumulus cells, intrafollicular peptides, steroids, *in vitro* maturation, cattle.

Introduction

There is great interest to improve efficiency of *in vitro* maturation of oocytes (IVM) in animal species and humans as IVM has been considered the main technological bottleneck to improve embryo *in vitro* production following *in vitro* fertilization (IVF). It has been clearly demonstrated that current IVM systems do not adequately reproduce the follicular environment where the cumulus-oocyte complex (COC) physiologically differentiates, which compromises cumulus cells function and oocyte developmental competence (Rizos *et al.,* 2002; Brown *et al.*, 2017). Therefore, understanding the mechanisms that regulate COC differentiation is critical for the improvement of IVM systems.

The bidirectional interaction between the oocyte and cumulus cells is essential for oocyte developmental competence and constitutes a valuable parameter for improving IVM/IVF outcomes (Gilchrist, 2011). A lot of attention has been given to secreted paracrine factors as mediators of the oocyte-cumulus communication, mainly to oocyte secreted factors (OSF). There is robust evidence that OSF, particularly bone morphogenetic protein 15 (BMP15) and growth differentiation factor 9 (GDF9), both members of the transforming growth factor-ß (TGF-ß) superfamily, and fibroblast growth factors (FGF) regulate various aspects of cumulus cells differentiation such as expansion, metabolism, steroidogenesis and apoptosis (Eppig, 2001; Sugiura *et al.*, 2007; Gilchrist *et al.*, 2008; Caixeta *et al.*, 2013b). However, data obtained in cattle and pigs suggest that the importance of OSF in the control of cumulus expansion and metabolism may vary between species (Buccione *et al.,* 1990; Vanderhyden, 1993; Ralph *et al.*, 1995; Sutton *et al.*, 2003; Caixeta *et al.*, 2013b). Although the other direction of the oocyte-cumulus communication has been less explored, there is recent evidence that cumulus derived peptides regulate nuclear maturation and gene expression in the oocyte (Lima *et al.*, 2016).

Apart from secreted factors, oocyte-cumulus communication is also mediated by transzonal cytoplasmic projections (TZP), which are extensions of cumulus cells that cross the zona pellucida transporting ions, metabolites and regulatory molecules (Albertini *et al.*, 2001). The delivery of glucose metabolites and small regulatory molecules through gap junctions connecting the end of the TZPs with the ooplasm appears crucial for the control of meiosis, chromatin configuration, transcriptional activity and metabolism of the oocyte (Conti *et al.*, 2012; Luciano *et al.*, 2014; Gilchrist *et al.*, 2016; Brown *et al.*, 2017). In addition to the transport through gap junctions, recent studies indicate that TZPs can also deliver larger molecules such as RNA transcripts via micro-vesicles in a transport mechanism designated as the gametic synapse (Macaulay *et al.*, 2014). In fact, cumulus-derived RNA has been identified in oocyte polyribosomes suggesting that the gametic synapse can influence the translational activity of the oocyte (Macaulay *et al.*, 2016).

This paper aims to review and discuss some of the recent data on paracrine mediators of the oocyte-cumulus interaction, as well as mechanisms regulating periovulatory differentiation of cumulus cells and oocyte nuclear maturation with potential practical implications for IVM.

Oocyte *vs.* cumulus secreted factors: who runs the show in the cow?

A large body of data produced in mice points to a leading role for the oocyte in the regulation of cumulus cells differentiation and metabolism (Matzuk *et al.,* 2002; Gilchrist *et al.*, 2008). However, studies using microsurgical removal of the oocyte from the COC and co-culture of oocytectomized COCs with secreting denuded oocytes indicate that OSF are needed for cumulus expansion in mice, but not in cattle, pigs or rats (Buccione *et al.*, 1990; Ralph *et al.*, 1995; Vanderhyden *et al.*, 2003). More recently, the same approach demonstrated that OSF also play a central role in the regulation of glycolytic activity of cumulus cells in mice (Sugiura *et al.*, 2005), whereas in cattle, utilization

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of oxygen, glucose, pyruvate and lactate by cumulus cells was not affected by removal of the oocyte (Sutton *et al.*, 2003). Taken together, these data point to differences between species with regard to the participation of the oocyte in cumulus differentiation, raising speculation that autocrine and paracrine signaling within the cumulus may be more influential in species other than the mouse. In mono-ovulatory mammals, the functional relevance of intra-cumulus TGF-ß signaling is controversial. Studies assessing the expression patterns of BMP15 and GDF9 in the COC are conflicting. While expression of BMP15 and GDF9 has been consistently detected in the oocyte, in cumulus cells it was observed in one but not all studies in cattle (Hosoe *et al.*, 2011; Crawford and McNatty, 2012).

Alternatively, FGF2 and Kit Ligand (KL) are two potential and less controversial cumulus-derived regulators of COC maturation. A microarray study pointed FGF2 as an important up-regulated gene in the predicted pathways activated by the LH surge to induce final differentiation of bovine cumulus cells (Assidi *et al.*, 2010). In addition, we have shown that transcription of FGFR2C and FGFR3C, two receptors efficiently activated by FGF2, is drastically and rapidly increased in cumulus cells from bovine COCs subjected to FSH-stimulated IVM, suggesting that sensitivity to FGF2 is enhanced with activation of the ovulatory cascade (Zhang *et al.*, 2006; Caixeta *et al.*, 2013a). Taken together, these studies indicate that FGF2 signaling is enhanced in preparation for ovulation and final COC maturation. In fact, recent data from our laboratory suggest the involvement of FGF2 in the regulation of meiosis progression, cumulus expansion and apoptosis (Buratini J.; 2017; Institute of Biosciences, São Paulo State University, Botucatu, SP, Brazil; unpublished data). Moreover, the involvement of FGF2 in the control of COC maturation is also consistent with our previous finding that FGF2 increases phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene homolog (PI3K/AKT) in granulosa cells, two pathways known to regulate meiotic resumption and cumulus expansion (Jiang *et al.*, 2011; Prochazka *et al.*, 2012).

On the other hand, we have recently reported that mRNA levels of KL increase around 10 times in bovine cumulus cells during FSH-stimulated IVM and presented evidence of a role for KL in the regulation of meiosis progression under the influence of OSF in cattle (Lima *et al.*, 2016). These data are compiled and discussed in further details below. Therefore, whilst further studies are needed to address the importance of cumulus derived peptides for COC maturation, the data collected so far suggest that OSF are less influential in the cow than in the mouse and that an interaction of oocyte and cumulus derived factors likely runs the show in the cow.

Oocyte secreted factors in the control of cumulus expansion and metabolism

Although OSF are not absolutely required for cumulus expansion in cattle, they appear to influence this process (Ralph *et al.*, 1995; Zhang *et al.*, 2010a; Caixeta *et al.*, 2013b). BMP15 and FGF10 are expressed by the oocyte and when added to the IVM medium they can enhance cumulus expansion and embryo production in cattle (Hussein *et al.*, 2006; Buratini *et al.*, 2007; Zhang *et al.*, 2010a; Crawford and McNatty, 2012). We have provided evidence that BMP15 and FGF10 control the expression of key genes in the ovulatory cascade. Supplementation of the IVM medium with BMP15 increased transcription of disintegrin and metalloprotease 10 (ADAM 10), ADAM 17, amphiregulin (AREG) and epiregulin (EREG) in cumulus cells from bovine COCs. Alternatively, treatment with FGF10 promptly increased mRNA levels of prostaglandin (PG)-endoperoxide synthase (PTGS2), and subsequently of pentraxin 3 (PTX3) and tumor necrosis factor alpha-induced protein 6 (TNFAIP6) in bovine cumulus cells (Caixeta *et al.*, 2013b). Therefore, BMP15 appears to enhance the ovulatory cascade right at its beginning by increasing production, cleavage and release of EGF-like factors, the last two events being a consequence of ADAM10 and ADAM17 activity (reviewed by Ben-Ami *et al.*, 2006). These effects of BMP15 are consistent with its positive impact on developmental competence in cattle (Hussein *et al.*, 2006) and with evidences of suboptimal EGF signaling in bovine COCs matured *in vitro* (Brown *et al.*, 2017). On the other hand, FGF10 would act downstream of EGF-like factors by increasing the expression of cross-linking proteins that stabilize the extracellular matrix (PTX3 and TNFAIP6). This appears to be at least in part mediated by the preceding prompt increase in PTGS2 expression, since PGE2 is required for TNFAIP6 expression (Ochsner *et al.*, 2003, reviewed by Russell and Robker, 2007). These findings are in agreement with the positive effect of FGF10 on embryo production following IVM/IVF and with higher expression of TNFAIP6 in cumulus cells from *in vivo* matured compared with *in vitro* matured bovine COCs (Tesfaye *et al.*, 2009; Zhang *et al.*, 2010a).

Despite the evidences that BMP15 and FGF10 act at different steps of the ovulatory cascade, they appear to act similarly with regard to their influence on glucose metabolism. They both increased glucose uptake without altering lactate production during IVM of bovine COCs, which was accompanied by increases in mRNA levels of glucose transporters (GLUT1 and GLUT4). Interestingly, BMP15 and FGF10 also increased mRNA abundance of glucosamine:fructose-6-PO_4 transaminases (GFPT1 and GFPT2) and hyaluronan synthase 2 (HAS2), which are rate-limiting enzymes in the hexosamine pathway of glucose metabolism that leads to the production of hyaluronic acid, the major component of the extracellular matrix (Sutton-McDowall *et al.*, 2010; Caixeta *et al.*, 2013b). Therefore, collectively, these data suggest that after the activation of the ovulatory cascade BMP15 and FGF10 direct the metabolism of glucose towards the synthesis of hyaluronic acid to support the formation of extracellular matrix for cumulus expansion.

Nevertheless, at earlier stages of COC maturation, before the activation of the ovulatory

cascade, the influence of BMP15 and FGFs on glucose metabolism may be different. BMP15 and FGF8 were shown to cooperate to increase the expression and activity of glycolytic enzymes phosphofructokinase (PFKP) and lactate dehydrogenase (LDHA) in cumulus cells from COCs arrested at the germinal vesicle (GV) stage in mice (Sugiura *et al.,* 2007). On the other hand, in bovine COCs undergoing IVM, the combination of BMP15 with FGF17, a member of the FGF8 superfamily also expressed by the bovine oocyte and capable of activating the same receptors that FGF8, did not alter PFKP mRNA levels in cumulus cells (Zhang *et al.*, 2006; Machado *et al.*, 2009, 2015). Therefore, additional studies dissecting the influence of species, COC developmental stage and culture conditions are needed for a clearer understanding of the roles of OSF in the regulation of glucose metabolism in the COC.

Like FGF10, FGF17 was shown to enhance expansion of bovine COCs during IVM (Machado *et al.*, 2015). However, FGF17 did not alter the expression of PTGS2, or any of the genes in the ovulatory cascade investigated [ADAM10, ADAM17, AREG, EREG, PTX3, TNFAIP6, VERS (versican) and HAS2]. Therefore, different FGFs appear to impact on cumulus expansion and differentiation through different mechanisms. Although no additional effect on cumulus expansion or meiosis progression was observed when FGF17 was combined with BMP15 during IVM, this combination increased mRNA levels of the nuclear progesterone receptor (nPR) in cumulus cells after IVM, as well as the number of cells in the inner cell mass (ICM) of blastocysts produced by IVF/IVC (Machado *et al.*, 2015). These data therefore suggest that FGFs and BMP15 interact during COC maturation to improve developmental competence, which may be at least in part a consequence of increased progesterone sensitivity. Previous studies using inhibitors of progesterone synthesis and nPR antagonists have elegantly demonstrated that progesterone signaling is crucial for cumulus expansion and oocyte developmental competence (Aparicio *et al.*, 2011).

Oocyte and cumulus-derived factors in the regulation of nuclear maturation and cumulus-oocyte communication

A major and well recognized limitation of IVM is the asynchrony between oocyte nuclear and cytoplasmic maturation. Chromatin condensation is precipitated and transcriptional activity diminishes abruptly when the COC is removed from the follicle (Hyttel *et al.*, 1987; Lodde *et al.*, 2007). Therefore, pre-IVM cultures containing agents capable of delaying nuclear maturation such as natriuretic peptide precursor C (NPPC) and phosphodiesterase inhibitors have been proposed to improve the outcomes of IVM/IVF in cattle (Albuz *et al.*, 2010; Franciosi *et al.*, 2014), although these strategies have not yet provided consistent results in different breeds and laboratories (Gilchrist *et al*., 2015).

Robust studies using Nppc and Npr2 (natriuretic peptide receptor B) mutant mice first demonstrated the importance of NPPC signaling for meiotic arrest. A model has been proposed and widely accepted in which NPPC produced predominantly by mural granulosa cells activates natriuretic peptide receptor B (NPR2) on cumulus cells to induce production of cGMP, which is then transferred to the oocyte through gap junctions, deviating the activity of phosphodiesterase 3 from cAMP. This would maintain cAMP at levels required to prevent the synthesis of maturation promoting factor (MPF), thus holding the oocyte in meiotic arrest (Zhang *et al.*, 2010b; Conti *et al.*, 2012). Later studies demonstrated that NPPC is expressed by bovine cumulus cells, and that, like in the mouse, NPPC also inhibits germinal vesicle breakdown (GVBD) in cattle (Franciosi *et al.*, 2014; De Cesaro *et al.*, 2015). For meiosis resumption to occur, LH inhibits NPPC production by granulosa cells and reduces the flow of cGMP from the outer layers of the cumulus to the oocyte (Kawamura *et al.*, 2011; Shuhaibar *et al.*, 2015). Reduced gap junction functionality after the LH surge is believed to be a consequence of the production/secretion of EGF-like peptides that bind to the EGFR to induce mitogen activated protein kinase (MAPK) dependent phosphorylation of connexins, the main components of gap junctions (Conti *et al.*, 2012).

Therefore the influence of NPPC on nuclear maturation depends on the functionality of gap junctions between cumulus cells and the oocyte. The importance of gap junction mediated communication for meiotic arrest and developmental competence was unequivocally demonstrated by studies where chemically induced gap junction uncoupling led to chromatin condensation and decreased transcriptional activity in the bovine oocyte (Luciano *et al.*, 2011). And since these effects were neutralized by co-treatment with cilostamide, an oocyte specific phosphodiesterase inhibitor, it was concluded that the impact of gap junction functionality is mediated by intra-oocyte cAMP. This is in agreement with a later study from the same group reporting positive effects of NPPC and cilostamide on gap junction functionality in cattle (Franciosi *et al.*, 2014).

Interestingly, the influence of NPPC appears to be regulated by intrafollicular steroids. In mice, estradiol is required to maintain the ability of NPPC to stimulate cGMP production and to prevent GVBD in culture, and both estradiol and testosterone can increase mRNA levels of Npr2 in cumulus cells (Zhang *et al.*, 2011). The enhancement of NPPC action by steroids also occurs in cattle. We have recently demonstrated that intrafollicular steroids cooperate with NPPC to slow nuclear maturation and to increase gap junction mediated cumulus-oocyte communication in the bovine COC. More specifically, co-treatment with estradiol, progesterone and adrostenedione at physiological concentrations enhanced the ability of NPPC to inhibit GVBD and to increase the transfer of a dye from the oocyte to cumulus cells, which was accompanied by an increase in NPR2 mRNA levels. Therefore, the enhanced effects on nuclear maturation and gap junction functionality were interpreted as a consequence of greater NPPC signaling and cGMP production in the

presence of steroids. Moreover, the combination of NPPC with follicular steroids in a pre-IVM culture promoted improved embryo quality (assessed by total cell number), suggesting that this strategy may be useful to improve IVM/IVF outcomes (Soares *et al.*, 2017).

The NPPC system is also regulated by cumulus and oocyte-derived factors. We have recently reported evidence of a link between NPPC and KL under the influence of OSF in cattle. In mammals, Kit ligand is expressed by granulosa cells since very early stages of folliculogenesis and activates the receptor KIT on the oocyte and theca cells (Hutt *et al.*, 2006; Thomas and Vanderhyden, 2006). The roles of KL signaling in periovulatory COC differentiation have not been deeply investigated and are controversial; KL delayed 1st polar body extrusion in rats (Ismail *et al.*, 1997), but did the opposite in mice (Ye *et al.*, 2009). In cattle, first we demonstrated that mRNA levels of both isoforms of KL, KL1 and KL2, increase during the first 12 h of FSH-stimulated IVM in cumulus cells, suggesting that KL transcription is enhanced in preparation for ovulation. Secondly, we observed that KL supplementation during IVM of bovine COCs does not affect cumulus expansion, but enhances oocyte maturation as assessed by the percentage of oocytes reaching metaphase II. To investigate the mechanisms by which KL impacts on nuclear maturation, we assessed its effects on the expression of genes regulating meiosis in the bovine COC. Kit ligand did not alter mRNA levels of NPR2, but decreased mRNA abundance of NPPC in bovine cumulus cells. In addition, KL increased expression of Y-box binding protein 2 (YBX2) in the oocyte, a protein that regulates RNA stability and protein synthesis and is required for normal spindle formation (Medvedev *et al.*, 2011). Finally, we assessed whether the oocyte regulates KL expression in cumulus cells using the oocytectomy model, and observed mRNA levels around 5 times more abundant in oocytectomized compared with intact COCs at the end of IVM. The increase in KL expression was completely abrogated by co-culture with denuded oocytes, indicating that the influence of the oocyte on KL expression is mediated by OSF. Conversely and in agreement with the inhibitory influence of KL on NPPC expression described above, oocytectomy markedly decreased mRNA levels of NPPC in cumulus cells. The specific OSF that mediate the effects of KL on cumulus NPPC expression appear to vary between species and remain to be completely identified. In our studies, treatment with FGF10 during IVM decreased KL2 mRNA expression, suggesting that FGF10 may be one of these OSF in cattle (Lima *et al.*, 2016). Taken together, these data suggest that the oocyte and cumulus derived factors interact to control meiosis. It is tempting to speculate that an increase in cumulus KL expression overcoming the inhibitory effect of the oocyte through NPPC signaling may be part of the mechanisms leading to meiosis resumption in the periovulatory period in cattle.

Concluding remarks

In this mini-review we compile data indicating that oocyte and cumulus derived factors interact to regulate cumulus differentiation, nuclear maturation and oocyte developmental competence in cattle. In addition, we present published evidence that steroids modulate the influence of cumulus-derived factors on meiosis progression and cumulus-oocyte communication. The data compiled herein widens our view of the mechanisms that regulate meiosis and cumulus function in cattle, and represent useful parameters for the improvement of IVM/IVF outcomes.

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