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Interleukin-1β and TNF-α systems in ovarian follicles and their roles during follicular development, oocyte maturation and ovulation

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Review

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Summary

Tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) are cytokines that are involved in the development, proliferation and apoptosis of ovarian follicular cells in domestic mammals. The expression of these cytokines in various follicular compartments, depending on the stage of follicle development, demonstrates their involvement in the control of primordial follicle growth up to the preovulatory stage. The mechanism of action of these factors depends on the presence of their receptors that transduce their biological actions. This review shows the expression sites of TNF-α, IL-1β and their receptors in ovarian follicles, and discusses the mechanism of action of these cytokines during follicle development, oocyte maturation and ovulation in domestic animals.

Introduction

Ovarian follicular development involves a complex series of coordinated events, including primordial follicle activation, growth of primary and secondary follicles, formation of antrum cavity, oocyte maturation, steroidogenesis and ovulation (Van Den Hurk and Zhao, 2005; Silva *et al.*, 2009, 2016; Figueiredo *et al.*, 2018). During these growth and differentiation processes, paracrine factors mediate the communication among oocyte, granulosa and theca cells (Hsueh *et al.*, 2015). Cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) are involved in controlling follicular development and ovulation. Their functions include regulation of cellular proliferation/differentiation, follicular survival/atresia, and oocyte maturation (Field *et al.*, 2014).

TNF-α is a cytokine that was originally recognized for its action in inflammatory processes (Terranova and Rice, 1997). This factor acts by binding to one of its two receptors, namely a type I receptor (TNFR1), which is approximately 60 kDa and a type II receptor (TNFR2). Moreover, TNF-α is involved in the regulation of physiological processes such as follicular development, steroidogenesis, ovulation and corpus luteum function (Sakumoto and Okuda, 2004; Glister *et al.*, 2014; Samir *et al.*, 2017). It has also been reported that, depending on the stage of development, TNF-α may regulate differentiation of granulosa cells (Glister *et al.*, 2014) and apoptosis (Manabe *et al.*, 2008).

IL-1β is another important pro-inflammatory cytokine that can stimulate T-cell proliferation and increase antibody production (Kool *et al.*, 2012). IL-1β synthesis occurs primarily in macrophages and monocytes when stimulated, but may be synthesized to a lesser extent in other cell types such as lymphocytes, neutrophils, fibroblasts, and endothelial cells (Gabay *et al.*, 2010). Passos *et al.* (2016) also reported that IL-1β and its receptors are expressed in bovine ovarian follicles at various stages of development. The IL-1 system has two receptor types, i.e. a type I receptor (IL-1RI) with a 213 amino acid domain in the intracytoplasmic region and a type II receptor (IL-1RII) with only a domain of 29 residues (Adashi, 1998). IL-1RII and IL-1R antagonist (IL-1Ra) are natural inhibitors that prevent excessive inflammatory responses caused by the IL-1 system (Gabay *et al.*, 2010). It has been demonstrated that IL-1β acts in the control of follicle development by facilitating granulosa cells proliferation and preventing premature differentiation (Brännström, 2004). This factor also influences apoptosis in ovarian granulosa cells (Chun *et al.*, 1995) and appears to be involved in a number of ovulation-associated events such as protease synthesis, regulation of plasminogen activator activity, and prostaglandin production (Brännström, 2004). Considering that TNF-α and IL-1β are produced locally in the ovary and, once secreted, diffuse to act in a paracrine/autocrine manner to regulate ovarian function, it is very important to discuss recent findings about these cytokines to better understand their role in ovarian folliculogenesis in domestic animals.

The review aims to show the expression sites of TNF-α and IL-1β system members in the ovary and to discuss their roles and mechanisms of action during follicle development, oocyte maturation and ovulation in domestic animal species.

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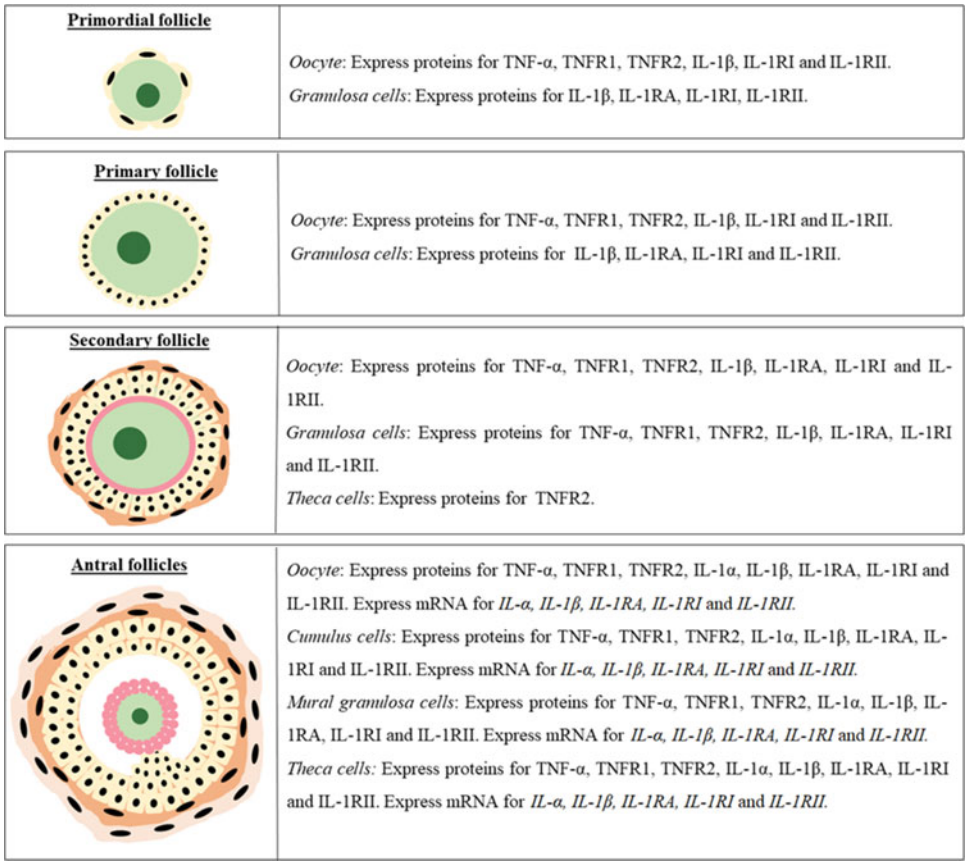

Figure 1. Expression of proteins of IL-1β, TNF-α and their receptors in bovine ovarian follicles.

Expression of TNF-α systems in ovarian follicles and its mechanism of action

The non-inflammatory effects to which TNF-α is related include control of follicular development (Samir *et al.*, 2017), ovulation, and, depending on its mechanism of action, it may further regulate differentiation (Glister *et al.*, 2014) or apoptosis (Manabe *et al.*, 2008). In bovine ovaries, Silva *et al.* (2017b) showed that TNF-α system proteins (TNF-α/TNFR1/TNFR2) are expressed in various follicular compartments. These authors reported the presence of TNF-α and TNFR1 in primary follicle oocytes, as well as in oocyte, granulosa and theca cells of secondary and antral follicles. TNFR2 proteins are expressed in oocytes of primordial, primary and secondary follicles, as well as in granulosa and theca cells of secondary and antral follicles. TNF-α receptor expression was demonstrated in granulosa cells from small (1–5 mm) and large (> 8 mm) bovine antral follicles (Spicer, 2001). In addition, mRNA and/or protein for TNF-α are also localized in different follicular compartments of sheep preovulatory follicles (Johnson *et al.*, 1999). Human oocytes and cumulus cells from large antral follicles express both mRNA and protein for TNF-α and its TNFR2 receptor (Naz *et al.*, 1997). In pig antral follicles, intense signals for TNF-α and its mRNAs were demonstrated in granulosa cells (Nakayama, 2003). In rat ovaries, TNF-α localization sites include oocytes (Marcinkiewicz *et al.*, 1994), granulosa cells (Roby and Terranova, 1989), corpora lutea and macrophages (Sancho-Tello *et al.*, 1993). In rabbits, TNF-α production and accumulation were reported in the corpus luteum of pseudopregnant and pregnant animals. These data highlight an autocrine and paracrine effect of TNF-α during follicular development. Figure 1 summarizes the sites of expression of TNF-α system in ovarian follicles.

TNF-α acts by binding to one of its two receptors, i.e. TNFR1 or TNFR2. These receptors are transmembrane proteins with cytoplasmic domains that initiate signal transduction after TNF-α binding (Fig. 2). After activation of TNFR1, signalling begins with the recruitment of various adapter proteins to form complex I, consisting of TNFR1-associated DEATH domain protein (TRADD), TNF-associated factor 2 (TRAF2), and the interacting receptor with protein 1 (RIP1). Then, complex II is formed by association of complex I plus Fas-associated death domain (FADD) and pro-caspase 8/10, which are responsible for apoptosis (Micheau and Tschopp, 2003; Wullaert *et al.*, 2007). However, the TRADD protein that interacts with the intracellular domain of TNFR1 can be suppressed by the *crmA* gene (Hsu *et al.*, 1995). In addition, TNFR1 receptor may also activate transcription factor nuclear factor-kappaB (NF-κB) and promote cell survival by permanence of the caspase-8 inhibitor (FLIP) (Micheau and Tschopp, 2003). The p65 (RelA), RelB, c-Rel, p50/p105 and p52/p100 members of the NF-κB family appear in cells as homodimers or heterodimers linked to IκB proteins (Hayden and Ghosh, 2004). NF-κB factor, when not stimulated, is bound to IκB (one of the NF-κB inhibitory proteins), as phosphorylation and degradation of IκB are required to promote translocation of NF-κB (p65 and p50) to the nucleus (Baeuerle and Baltimore, 1996). After IκB kinase (IKK) stimulation, IKKα and IKKβ promote the classical pathway of NF-κB translocation to the nucleus (Rauert *et al.*, 2010). The classical pathway can be activated by both TNFR1 and TNFR2. The NF-κB modifier

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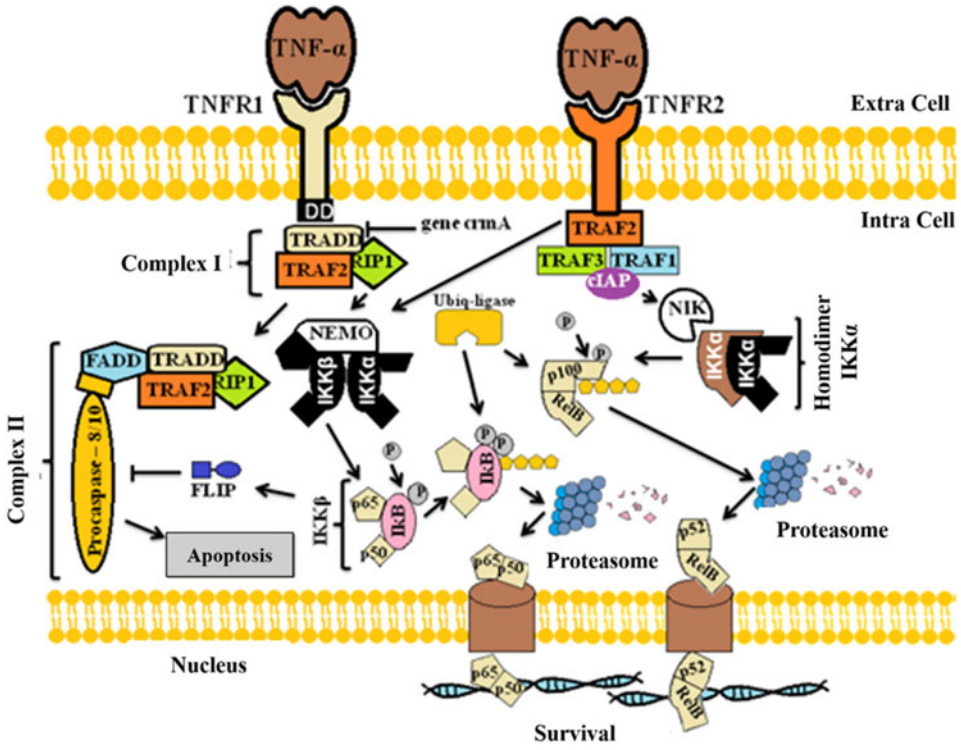

Figure 2. Mechanisms of action of TNF-α to promote cell signal transduction.

(NEMO) signals activate the IκB kinase complex beta subunit (IKKβ), which then phosphorylates the IκB protein into two N-terminal serine residues. This complex is recognized by ubiquitin ligase, leading to its activation. polyubiquitination and subsequent degradation by proteasomes (Fig. 2) (Hayden and Ghosh, 2004).

The alternative NF-κB pathway through phosphorylation of the IKKα complex (composed of p100 and RelB) is independent of NEMO stimulation (Sun and Ley, 2008). First, TNFR2 signals through TRAF2 that binds to TNF-associated factor 1 (TRAF1), TNF-associated factor 3 (TRAF3) and apoptosis inhibitor protein (cIAP) (ROTHE *et al.*, 1995). This complex activates the inducing kinase NF-κB (NIK), responsible for phosphorylation and activation of the IKKα homodimer (Senftleben *et al.*, 2001). Then, two IKKα C-terminals are phosphorylated for proteosomal degradation, generating p52 that is translocated to the nucleus (Fig. 2) (Rauert *et al.*, 2010). Studies suggest that the classical and alternative pathways of NF-κB have distinct regulatory functions (Bonizzi and Karin, 2004).

Expression of IL system in ovarian follicles and its mechanisms of action

In bovine species, Passos *et al.* (2016) showed that IL-1β protein is expressed in oocytes and granulosa cells of primordial follicles, as well as in oocyte, granulosa and theca cells from primary, secondary and antral follicles. These authors showed that the protein for IL-1RA is found in granulosa cells of primary follicles and in oocyte and granulosa cells of secondary and antral follicles. Oocytes and granulosa cells from primordial and primary follicles express IL-1RI, while this protein is found in oocyte, granulosa and theca cells from secondary and small antral follicles. For IL-1RII, the protein is observed in oocytes and granulosa cells of all follicular categories. Figure 1 summarizes the sites of expression of IL-1β system in ovarian follicles.

IL-1β was previously demonstrated in oocytes, granulosa, theca and cumulus cells in ovaries of human (Zolti *et al.*, 1991; Barak *et al.*, 1992; De Los Santos *et al.*, 1998; Carlberg *et al.*, 2000), mouse (Simón *et al.*, 1994; Terranova and Rice, 1997), rat (Brännström *et al.*, 1994) and mare (Martoriati *et al.*, 2002). IL-1α protein was previously detected in mouse (Simón *et al.*, 1994; Terranova and Rice, 1997) and human (De Los Santos *et al.*, 1998) oocytes, theca and cumulus cells (Kol *et al.*, 1999), showing that ovarian cells synthesize IL-1α. Moreover, IL-1β was found to be produced by ovarian granulosa cells of preovulatory follicles (Salamonsen *et al.*, 2007; Trundley and Moffett, 2004). The presence of IL-1RA was demonstrated in granulosa and cumulus cells of mares (Martoriati *et al.*, 2002) and human (De Los Santos *et al.*, 1998). The presence of IL-1RI protein was previously demonstrated in oocytes, granulosa, theca and cumulus cells in ovarian tissues of mouse (Simón *et al.*, 1994), rat (Kol *et al.*, 1999; Wang *et al.*, 1997), human (De Los Santos *et al.*, 1998; Wang *et al.*, 1997) and mares (Martoriati *et al.*, 2002). In mouse, the expression of IL-1RI varies with follicular development (Terranova and Rice, 1997). In human, it has been demonstrated that mRNA for IL-1RI is absent in primordial follicles, but present in granulosa and theca cells from growing secondary and antral follicles (Wang *et al.*, 1997).

In bovine follicles, Passos *et al.* (2016) reported that the growth from secondary to small antral follicles is followed by an increase in the levels of mRNA for IL-1α, IL-1β and IL-1RA (Fig. 1). In equine species, Martoriati *et al.* (2002) reported the presence of IL-1β and IL-1RI transcripts in oocytes of antral follicles, while transcripts for IL-1β, IL-1RA, IL-1RI and IL-1RII were found in cumulus cells. Other studies have shown that the members of the IL-1 system are located in various types of ovarian cells, i.e. in oocytes,

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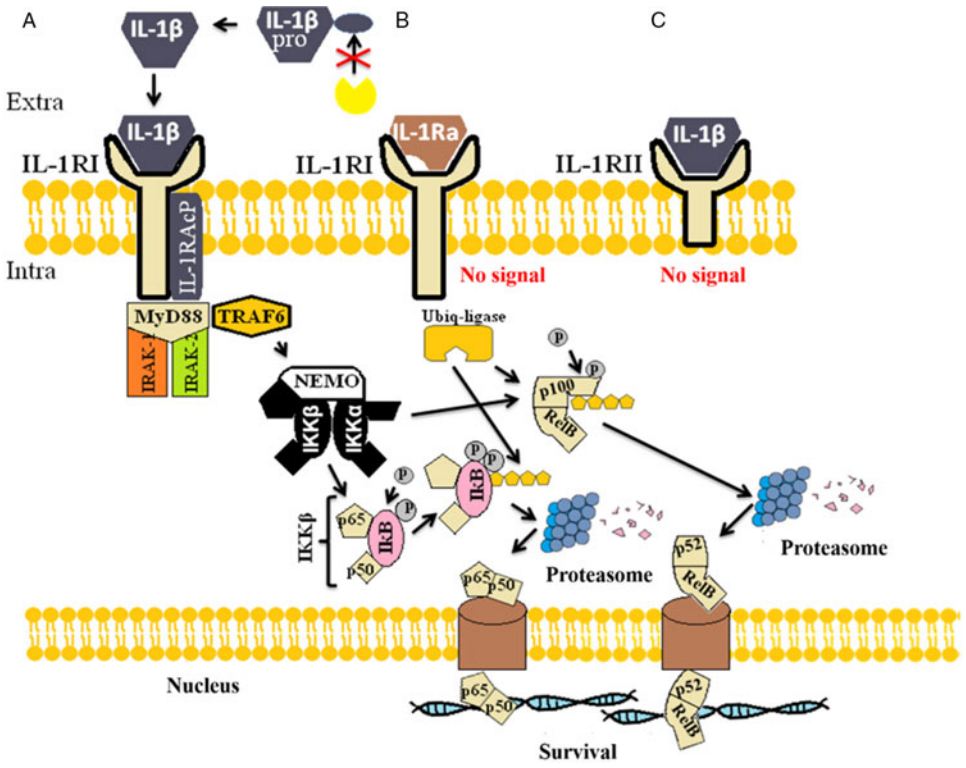

Figure 3. Mechanisms of action of IL-1β to promote cell signal transduction. (a) IL-1β system heterodimer complex capable of promoting signal transduction (classical pathway by NEMO stimulation). (b) Natural IL-1β antagonist (IL-1Ra) promoting blockade of signal transduction. (c) Type II receptor (IL-1RII) inhibiting signal transduction by the small peptide chain that does not cross the membrane completely.

granulosa and theca cells of several mammalian species (Sirotkin, 2011). The transcript for IL-1β is located in mural granulosa cells, the most inner layers of the theca, and in the oocytes of rat preantral and early antral follicles (Kol *et al.*, 1999). *IL-1RI* mRNA is also expressed in murine oocytes (Deyerle *et al.*, 1992) and abundant levels of *IL-1RA* mRNA are found in the granulosa of rat primordial and growing follicles (Wang *et al.*, 1997). Within antral follicles, Passos *et al.* (2016) showed that the follicular wall is the main site of production of mRNA for IL-1α, IL-1β, IL-1RA and IL-1RI. With the growth from small to large antral follicles, a reduction in expression of mRNA for IL-1α is observed but, in general, large follicles had higher expression of IL-1β, IL-1RA and IL-1RII. Other studies have shown that mare cumulus–oocyte complexes (COCs) contain *IL-1β* mRNA (Martoriati *et al.*, 2002), and that the protein for IL-1β is secreted by cultured human granulosa cells (Carlberg *et al.*, 2000). Production of IL and their receptors is also observed in both granulosa and theca cells, while maximal production occurred in preovulatory follicles after gonadotropin action (Ingman and Jones, 2008).

Regarding the IL mechanism of action (Fig. 3), there are inhibitors, such as IL-1 receptor antagonist (IL-1Ra) and type II receptor (IL-1RII) that regulates the responses to IL-1β (Dinarello, 2010). In humans, IL-1β binds to two receptor types, a type I (IL-1RI) and a type II receptor (IL-1RII) (Adashi, 1998). IL-1RII and IL-1R antagonist (IL-1Ra) are natural inhibitors that prevent excessive inflammatory responses caused by the IL-1 system (Gabay *et al.*, 2010). Additionally, it was shown that IL-1RA blocks IL-1β mechanisms (Martoriati *et al.*, 2003a). The IL-1β receptor is a complex formed by the type I receptor and an accessory receptor protein (IL-1RAcP) that form an IL-1 heterodimer (Boraschi and Tagliabue, 2013). Myeloid differentiation protein (MyD88) is an molecule that acts as a transient adapter or regulator in the IL-1R signalling complex (Muzio *et al.*, 1997) and is capable of recruiting interleukin receptor-associated kinase type 1 (IRAK1) and type 2 (IRAK2) (Wesche *et al.*, 1997). In addition, receptor-associated factor 6 (TRAF6) is recruited by IL-1R and requires MyD88 to activate NF-κB (Wu and Arron, 2003). The classical NF-κB pathway occurs with the phosphorylation of two serine residues (ser32 and ser36) of the IκB protein by IκB kinase activity (IKK), the polyubiquitination of IKKβ and then degradation by the 26S proteosome, releasing NF-κB dimers (p65 and p50) (Nishikori, 2005; Karin and Ben-Neriah, 2000). IKKβ-dependent activation of NF-κB plays an important role in the transcriptional control of acute and chronic inflammation (Bonizzi and Karin, 2004). However, studies show that IL-1-induced, but not TNF-α induced, NEMO and IKKα are sufficient for NF-κB activation without requiring the IKKβ dimer (Solt *et al.*, 2007). Therefore, IL-1 can induce both the classical pathway through IKKβ and IKKα through NEMO (Solt *et al.*, 2007; Bonizzi and Karin, 2004; Nishikori, 2005). Following activation by the IKKα complex, there is the transfer of p52 and RelB to the nucleus (Rauert *et al.*, 2010) and the IKKβ complex translocation of p65 and p50 (Baeuerle and Baltimore, 1996).

Effects of TNF-α during folliculogenesis, oocyte maturation and ovulation

Silva *et al.* (2017b) showed that that TNF-α increases the number of apoptotic cells in cultured bovine ovarian tissue and reduces primordial follicle survival. Other studies reported that TNF-α

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induces oocyte, granulosa and luteal cell death (Chen *et al.*, 1993; Kaipia *et al.*, 1996; Sasson *et al.*, 2002; Abdo *et al.*, 2003), as well as apoptosis in granulosa cells of rat preovulatory follicles (Sasson *et al.*, 2002). In mice, Nilsson *et al.* (2006) demonstrated that TNF-α can interact with P4 to regulate the growth of primordial follicles. In bovine secondary follicles *in vitro*, Paulino *et al.* (2018) showed that TNF-α promotes growth, antrum formation and maintains the ultrastructure of secondary follicles *in vitro*. These studies show that the effect of TNF-α on ovarian cells is dependent on the stage of follicle development, which can be associated with different levels of TNF-α receptor expression (Witty *et al.*, 1996). The ability of TNF-α to promote the increase in follicular diameter could be because these follicles have receptors (TNFR1 and TNFR2) for TNF-α in their oocyte and granulosa cells (Silva *et al.*, 2017b). Exogenous TNF-α added into culture medium can bind to the TNFR2 and promote follicular growth, instead of apoptosis. As reported by Wajant *et al.* (2003), TNFR2 can induce gene transcription associated with cell survival, growth and differentiation. Fischer *et al.* (2011) showed that protection from cell death is dependent on TNFR2 activation of the PI3K–PKB/Akt pathway. TNF-α has also been shown to activate NF-κB, which in turn regulates the expression of proteins associated with cell survival and cell proliferation (Aggarwal *et al.*, 2004).

TNF-α can also modulate steroidogenesis by granulosa, thecal and luteal cells (Chun and Hsueh, 1998), as some studies reported that TNF-α inhibits secretion of estradiol and P4 in murine, porcine, bovine and human granulosa cells *in vitro* (Spicer, 1998; Veldhuis *et al.*, 1991; Rice *et al.*, 1996). TNF-α also exerts an inhibitory effect on luteinization of pig granulosa cells and influences the balance between follicular growth (proliferation) and atresia (apoptosis) (Prange-Kiel *et al.*, 2001).

Regarding the effects of TNF-α on oocyte maturation, Ma *et al.* (2010) showed that exposure of porcine oocytes to TNF-α causes a reduction in oocyte maturation and abnormalities in chromosomal alignment. Conversely, in bovine species, this factor promotes *in vitro* oocyte growth during 48 h of culture of COCs from antral follicles and influenced the distribution of mitochondria in pre-matured oocytes (Lima *et al.*, 2018). TNF-α also reduces *CASP3* and *CASP6* mRNA levels in bovine cumulus cells after 12 h of culture (Silva *et al.*, 2017a). This fact suggests that, in bovine oocyte and cumulus cells, TNF-α is mainly acting by binding to the TNFR2, thereby reducing the apoptotic process. Silva *et al.*, (2017a) also showed that TNF-α reduces *HAS-2* mRNA levels in cumulus cells after culturing bovine COCs for 12 h, but this reduction in expression did not interfere with cumulus expansion at the end of maturation. Recently, Kong *et al.* (2018) showed that ageing mouse cumulus cells secrete TNF-α, which accelerates oocyte ageing by interacting with TNFR.

TNF-α is a mediator of ovulation in terms of oocyte release and death induction via apoptosis and autophagy of granulosa cells in ovarian tissue remodelling (Yamamoto *et al.*, 2015). Crespo *et al.* (2012) showed that luteinizing hormone (LH) induces ovulation via TNF-α-dependent increases in prostaglandin F2α. TNF-α is secreted by mammalian preovulatory follicles (Brännström *et al.*, 1994) and, in rats, its levels are increased by *in vivo* administration of hCG (Rice *et al.*, 1996). TNF-α enhances ovulation rates in rat ovary (Brännström *et al.*, 1994) and stimulates apoptosis (Murdoch *et al.*, 1997) and collagenolytic activity in preovulatory follicles (Johnson *et al.*, 1999).

Effects of IL-1 system members during folliculogenesis, oocyte maturation and ovulation

Regarding folliculogenesis, Passos *et al.* (2016) demonstrated that IL-1β promotes the development and activation of primordial bovine follicles and contributes to maintain early follicle survival. These findings suggest that IL-1β is a survival factor for bovine ovarian follicles, its action being partially mediated via NO and cGMP generation (Chun *et al.*, 1995). Previous studies have revealed that IL-1β controls the transition of follicular cells by facilitating their proliferation and differentiation (Brännström, 2004). For bovine secondary follicles, Paulino *et al.* (2018) showed that IL-1β does not influence their development *in vitro*. Probably, IL-1β acts mainly in large antral follicles. IL-1β is capable of promoting proliferation of bovine granulosa cells (Basini *et al.*, 1998) and suppressing apoptosis of rat ovarian follicles (Chun *et al.*, 1995), acting as a survival factor. Studies in murine (Karakji and Tsang, 1995) and bovine (Baratta *et al.*, 1996) species showed that the effects of IL-1 on granulosa cell proliferation *in vitro* are dependent on follicle size. IL-1β is also able to modulate steroidogenesis and promote the proliferation of granulosa cells in porcine (Fukuoka *et al.*, 1989) and human (Best and Hill, 1995) species. IL-1β promotes an increase in the production of cAMP, oestrogen, and progesterone in mice granulosa cells that are essential for growth and follicular development (Chun *et al.*, 1995). In contrast, Uri-Belapolsky *et al.* (2014) reported that IL-1β promotes apoptotic pathways and causes age-related exhaustion of ovarian reserves in mice.

In large antral follicles, intra-follicular injection of IL-1β in dominant follicles induces oocyte maturation *in vivo* (Martoriati *et al.*, 2003b). Chaubey *et al.* (2018) showed that IL-1β improves cumulus expansion and developmental ability of poor quality buffalo oocytes. In bovine species, IL-1β also improved the percentage of oocytes developing to the blastocyst stage. Recently, Javvaji *et al.* (2019) showed that IL-7 at low concentrations is beneficial for oocyte maturation, through the favourable level of intracellular reactive oxygen species and antioxidant mechanisms. Other studies have indicated that IL-7 promotes survival and multiplication of granulosa cells, germinal vesicle breakdown and quality and nuclear maturation of oocytes in murine species (Cakmak *et al.*, 2016; Franciosi *et al.*, 2016; Cheng *et al.*, 2011). Caillaud *et al.* (2005) showed that IL-1β alone is not able to promote cytoplasmic maturation of equine oocyte, but it may play an essential role in the physiology of equine oocytes by acting on meiosis resumption. Additionally, there is an important interdependence between IL-1α and follicle-stimulating hormone receptor (FSHR), as IL-1 receptor inactivation increases FSHR expression in rat granulosa cells (Uri-Belapolsky *et al.*, 2017). IL-1β reduces the expression of LH receptors in rat granulosa cells *in vitro* (Gottschall *et al.*, 1988) and promotes the switch in granulosa cell proliferation to differentiation (Karakji and Tsang, 1995), indicating that this cytokine participates in determining whether follicles undergo atresia or progress to ovulation. IL-1β can also upregulate granulosa cell and intraovarian macrophage nitric oxide (NO) production, thereby influencing cellular growth or apoptosis (Matsumi *et al.*, 2000).

Both IL-1β and TNF-α are known to induce ovulation in rats and rabbits (Machelon and Emilie, 1997). The acceleration of ovulation has been reported to occur by neutrophil infiltration

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into the theca cells layer, which induces IL-1β synthesis and promotes synergy to stimulate ovulation (Tanaka *et al.*, 2017). In mice and humans, *IL-1β* mRNA levels increase in granulosa cells as the follicle nears rupture (Machelon *et al.*, 1995; Adashi, 1998), emphasizing the role of IL-1β in ovulation. Furthermore, IL-1β modulates total prostaglandin E (PGE) production by granulosa cells, therefore providing a mechanism to determine the site of follicle rupture (Hurwitz *et al.*, 1991, 1992, 1995; Duffy *et al.*, 2019).

Final considerations

TNF-α and IL-1β systems are expressed in ovarian follicles of different species and influence follicular development, oocyte maturation and ovulation. TNF-α is related to cell growth and differentiation and apoptosis, depending on which receptors it binds. IL-1β is related to granulosa cell proliferation, acting on the transition of follicular cells and facilitating the process of differentiation and proliferation. Both TNF-α and IL-1β are also involved in the nuclear and/or cytoplasmic oocyte maturation process, as well as in mechanisms that determine follicle ovulation.

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