

## REVIEW

# The interleukin-1 system and female reproduction

N Gérard, M Caillaud, A Martoriati, G Goudet and A-C Lalmanach<sup>1</sup>

Physiologie de la Reproduction et des Comportements INRA-UMR 6073, Nouzilly, France

<sup>1</sup>Pathologie Infectieuse et Immunologie INRA 37380, Nouzilly, France

(Requests for offprints should be addressed to N Gérard; Email: gerard@tours.inra.fr)

### Abstract

Interleukins (ILs) are known best for their involvement in the immune system and their role during inflammation. In the ovary, a growing body of evidence suggests that the ovarian follicle is a site of inflammatory reactions. Thus ovarian cells could represent sources and targets of ILs. Since then, the IL-1 system components (IL-1 $\alpha$ , IL-1 $\beta$ , IL-1 receptor antagonist, IL-1 receptors) have been demonstrated to have several sites of synthesis in the ovary. These factors have been localized in the various ovarian cell types, such as the oocyte, granulosa and theca cells, in several mammalian species. IL-1-like bioactivity has been reported in human and porcine follicular fluid at the time

of ovulation. The role of IL-1 in local processes is still poorly known, although there is evidence for involvement in the ovulation process, and in oocyte maturation. More precisely, IL-1 may be involved in several ovulation-associated events such as the synthesis of proteases, regulation of plasminogen activator activity, prostaglandin and nitric oxide production. IL-1 also regulates ovarian steroidogenesis. These different aspects of the involvement of the IL-1 system in important aspects of female reproduction are discussed.

*Journal of Endocrinology* (2004) **180**, 203–212

### Introduction

Interleukins (ILs) are polypeptide cytokine components of the immune system that were originally defined by their action between leukocytes. IL-1 was first described in 1972 by Géry and Waksman (Géry & Waksman 1972). Identified as a lymphocyte-activating factor, it was named IL-1 in 1979 at the 2nd International Congress on Lymphokines. IL-1 is organized as a gene system that includes two bioactive ligands, IL-1 $\alpha$  and IL-1 $\beta$ , and one natural receptor antagonist (IL-1ra). These three molecules are encoded by separate genes and bind to two types of receptors: type 1 (IL-1R1) and type 2 receptors (IL-1R2). IL-1 is produced by a large variety of cells and acts as a paracrine/autocrine factor on target cells. Mice deficient in components of the IL-1 system are widely studied in order to better understand its implication in various physiological processes (Fantuzzi 2001). In the ovary, several studies led to the hypothesis that in mammalian species, IL-1 is a paracrine factor that could be involved in the cascade of events that lead to ovulation (Ben-Shlomo & Adashi 1994). This review focuses on the impact of the IL-1 system on ovarian function and physiology.

### The components of the IL-1 system

#### *IL-1 $\alpha$ and IL-1 $\beta$*

Cloning IL-1 showed that two separate genes encode two different types of IL-1. IL-1 $\alpha$  and IL-1 $\beta$  have been cloned in humans (March *et al.* 1985), mice (Lomedico *et al.* 1984, Gray *et al.* 1986), rats (Nishida *et al.* 1988), rabbits (Furutani *et al.* 1985, Mori *et al.* 1988) and horses (Howard *et al.* 1998). IL-1 $\alpha$  and IL-1 $\beta$  can either be stored in the cell after translation as a precursor (pro-IL-1) of 31 kDa. Pro-IL-1 $\alpha$  is as biologically active as the mature form. It acts intracellularly (Roux-Lombard 1998).

Mature forms are synthesized after cleavage of the precursor forms by IL-1-converting enzyme or caspase 1 (cysteine-containing proteinases cleaving behind aspartate). IL-1 $\alpha$  and IL-1 $\beta$  display amino acid and nucleotide homologies of 26 and 45% respectively in humans (Dower *et al.* 1986). Kurt-Jones *et al.* (1985) and Bailly *et al.* (1990) have demonstrated the existence of a transmembrane IL-1 $\alpha$  form of 23 kDa. This IL-1 $\alpha$  form is bioactive and was demonstrated at the surface of monocytes and B lymphocytes. This form is controversial (Minnich-Carruth *et al.* 1989), and it is generally admitted that IL-1 $\alpha$  and  $\beta$

are secreted molecules. Nevertheless, they do not contain a conventional peptide signal and the mechanism of their secretion is unknown (Rubartelli *et al.* 1990).

IL-1 $\alpha$  and  $\beta$  have similar biological effects. They play an essential role in the inflammatory process and the immune response. For example, they stimulate proliferation and activation of B and T lymphocytes, synthesis of acute phase proteins in the liver, and prostaglandin (PG) production (Oppenheim *et al.* 1986, Martin & Resch 1988, Dinarello 1991, Ribardo *et al.* 2001). IL-1 is mainly secreted by monocytes/macrophages after stimulation by various factors such as endotoxins.

Several publications demonstrate that IL-1 is produced by various tissues such as skin (Luger *et al.* 1981), brain (Giulan *et al.* 1988), testis (Khan *et al.* 1987), and lung, liver and placenta (Granholm & Söder 1991). Its presence has also been demonstrated in ovarian follicular fluid (Khan *et al.* 1988).

#### *IL-1ra*

IL-1ra was first detected in the urine of patients with fever or leukemia (Seckinger *et al.* 1987). Then, IL-1ra was detected in supernatants of human monocyte cultures (Eisenberg *et al.* 1990, 1991). IL-1ra regulates IL-1 bioactivity. Indeed, after binding to IL-1Rs, IL-1ra prevents IL-1 binding and does not transduce the intracellular signal. At present, it has been demonstrated that IL-1ra is produced by a large variety of cells, such as monocytes, macrophages, neutrophils, hepatocytes and microglia. Several studies have demonstrated that IL-1ra and IL-1 $\beta$  are produced by the same cell types, but this production activates different pathways (Granowitz *et al.* 1991, Vannier *et al.* 1992). It has been demonstrated that the IL-1ra gene shares 18% homology with IL-1 $\alpha$  and 26% homology with IL-1 $\beta$  (Carter *et al.* 1990). In humans, the IL-1ra gene is close to IL-1 $\alpha$  and IL-1 $\beta$  genes, which are localized on the long arm of chromosome 2. IL-1ra is a secreted glycosylated protein of 22 kDa (Hannum *et al.* 1990) which can bind to IL-1Rs with the same affinity as IL-1 (Arend & Guthridge 2000). The main function of IL-1ra is to regulate the effects of IL-1 by blocking receptors. This has been clearly demonstrated by using transgenic and IL-1ra knock-out mice (Arend & Guthridge 2000). An alternative splicing of the IL-1ra mRNA gives rise to a modification of the exon coding for the secretion sequence, leading to an intracellular isoform named icIL-1ra (Haskill *et al.* 1991, Butcher *et al.* 1994). Three icIL-1ra isoforms have been described. The biological activity of icIL-1ra 1 and 2 is the same as that of the secreted isoform of IL-1ra. In contrast, icIL-1ra 3 inhibits only slightly the IL-1 binding to its receptors (Arend & Guthridge 2000). IcIL-1ra is expressed constitutively in some cell types, and it has been suggested that icIL-1ra could play a regulatory role in IL-1 $\alpha$  bioactivity (Haskill *et al.* 1991).

#### *IL-1Rs*

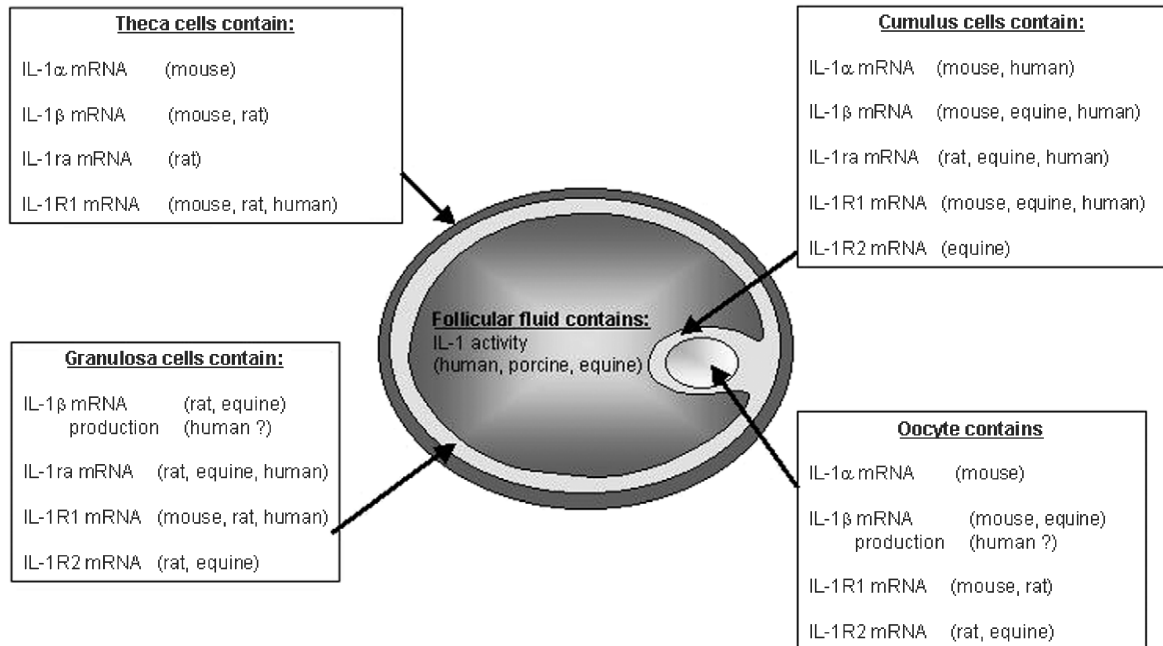
IL-1 $\alpha$ , IL-1 $\beta$  and IL-1ra bind to membrane receptors localized on target cells (Dower *et al.* 1986). Two kinds of receptors from the immunoglobulin family have been described. These two receptors are from two different genes but display similarities in their transmembrane and extracellular domains (Martin & Falk 1997). IL-1R1 is a 80 kDa glycoprotein. It was described in 1985 by Dower and colleagues (Dower *et al.* 1985). Its complete sequence contains 567 amino acids with a cytoplasmic part of 213 amino acids (Slack *et al.* 1993, Sims *et al.* 1994). It is expressed by various cell types, such as T cells (Dower *et al.* 1990), fibroblasts (Dower *et al.* 1990) and smooth muscle cells (Cavaillon 1991). IL-1R1 mainly binds IL-1 $\alpha$ , pro-IL-1 $\alpha$  and IL-1ra. It has only a low affinity for IL-1 $\beta$  (Kilian *et al.* 1986). IL-1R2 has a molecular mass of 60–65 kDa (Matsushima *et al.* 1986, MacMahan *et al.* 1991). Its complete sequence contains 398 amino acids, with a small intracytoplasmic part of 29 amino acids (Slack *et al.* 1993). Thus, several authors have confirmed that IL-1R2 is not able to transduce the signal (Sims *et al.* 1993) and would only participate in the bioavailability of ligands such as IL-1 $\beta$  (Colotta *et al.* 1994). This receptor is expressed by B and T cells, monocytes and placenta (Cavaillon 1991), as well as in the mouse brain (Gabellec *et al.* 1996). IL-1R2 displays a higher affinity for IL-1 $\beta$  than for IL-1 $\alpha$  (Roux-Lombard 1998). The IL-1 biological activity regulation is complex because soluble forms of receptors have been described (Symons *et al.* 1991). These soluble receptors result from a proteolytic cleavage of the extracellular part of membrane receptors. They inhibit, by binding IL-1 extracellularly, the binding of IL-1 to membrane receptors, and thus act as inhibitory factors since no signal is transmitted within the cell. It has been demonstrated that the soluble form of type 1 receptor preferentially binds to IL-1 $\alpha$  and IL-1ra, whereas the soluble form of type 2 receptor binds to IL-1 $\beta$  with a higher affinity (Roux-Lombard 1998).

#### **The IL-1 system in the ovary**

The ovarian expression sites of the IL-1 members have been studied in several species (Machelon & Emilie 1997). Some contradictory results have been obtained, suggesting some species-specific features. The potential production sites for the IL-1 system components are summarized in Fig. 1.

#### *IL-1 $\alpha$ and IL-1 $\beta$*

In 1988, some IL-1 biological activity was measured for the first time in human follicular fluid (Khan *et al.* 1988). This result has been then confirmed in humans (Barak *et al.* 1992, Wang & Norman 1992, Jasper & Norman 1995)



**Figure 1** Localization of the IL-1 system components in the ovarian follicle of mammalian species. Related gene expression and/or protein production are shown according to data available in the literature. (?) indicates controversial results.

and pigs (Takakura *et al.* 1989). This biological activity could result in part from some local IL-1 production by ovarian cells (granulosa and/or theca cells). De Los Santos *et al.* (1998) demonstrated in women involved in *in vitro* fertilization trials that cumulus cells express IL-1 $\alpha$  and IL-1 $\beta$  mRNA. This observation confirms the study performed by Barak *et al.* (1992). Recently, Carlberg *et al.* (2000) have confirmed that human granulosa cells secrete IL-1 $\beta$  *in vitro*. These results contrast with a previous study showing that human granulosa and theca cells do not contain mRNA coding for IL-1 $\beta$  (Hurwitz *et al.* 1992). These conflicting observations could be explained by the high individual variability among the cells from the women participating in these studies. Some recent work has shown a correlation between intrafollicular levels of IL-1 and the quality of the oocyte in terms of embryos after *in vitro* fertilization (Karagouni *et al.* 1998, Mendoza *et al.* 1999). Finally, IL-1 $\beta$  mRNA and proteins have been localized in human embryos at the time of fertilization, suggesting their presence in the mature oocyte (De Los Santos *et al.* 1996). This study confirms the results obtained by Zolti *et al.* (1991), who showed some IL-1 bioactivity in culture media from human oocytes, cumulus cells and embryos. In the mouse, the ovarian synthesis of IL-1 $\alpha$  and IL-1 $\beta$  was first detected by *in situ* hybridization (Takacs *et al.* 1988). Patterns change during follicular development. IL-1 $\alpha$  and  $\beta$  are first observed in the theca interna from growing follicles and in the oocyte (Simon *et al.* 1994, Terranova & Montgomery-Rice 1997). At the time of preovulatory maturation, after the luteinizing

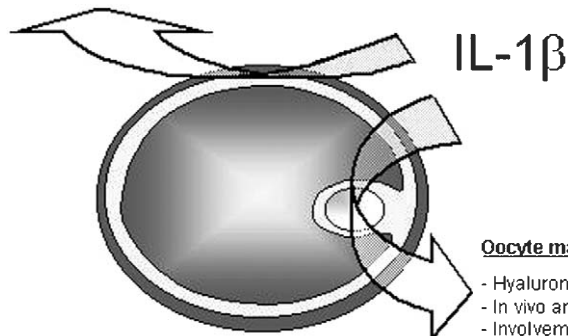
hormone (LH) surge or human chorionic gonadotropin (hCG) injection, high levels of IL-1 $\alpha$  and IL-1 $\beta$  are observed in cumulus cells (Simon *et al.* 1994). In rats, IL-1 $\beta$  mRNA was localized by *in situ* hybridization in theca cells after hCG injection (Hurwitz *et al.* 1991). This result was confirmed by Kol *et al.* (1999a). In the same study, these authors showed the presence of IL-1 $\beta$  mRNA in granulosa cells, and demonstrated the existence of an intrafollicular IL-1 $\beta$  surge at the time of ovulation as previously demonstrated by Brännström *et al.* (1994). They also demonstrated that ovarian cells synthesize IL-1 $\alpha$  and that this production is IL-1 $\beta$ -dependent (Kol *et al.* 1999b). Recently, we demonstrated the presence of IL-1 $\beta$  mRNA in equine cumulus–oocyte complexes (Martoriati *et al.* 2002). The IL-1 $\beta$  mRNA level varies during *in vivo* and *in vitro* maturation (Martoriati *et al.* 2002). Moreover, IL-1 $\beta$  mRNA has been demonstrated in equine granulosa cells, whereas immunoreactive IL-1 $\beta$  has been observed in follicular fluids from preovulatory follicles (Martoriati & Gérard 2003).

#### IL-1ra

Only few studies have addressed the localization of the IL-1 receptor antagonist in the ovary. In 1992, RNA extraction from human ovarian fragments allowed for the first time the detection of IL-1ra mRNA in this tissue (Hurwitz *et al.* 1992). More precisely, these authors demonstrated that human granulosa cells totally devoid of immune cells synthesize IL-1ra. Then, IL-1ra was

**Inflammatory events and ovulation:**

- Collagenases/metalloproteases synthesis
- PAI synthesis and PA inhibition
- Progesterone and estradiol-17 $\beta$  synthesis
- COX-2 activity, PGE2 and PGF2 $\alpha$  synthesis
- NO production
- Decrease in FSH receptors



**Figure 2** A summary of the potential roles of IL-1 $\beta$  in the mammalian ovarian follicle. PAI, plasminogen activator inhibitors; PA, plasminogen activator; COX-2, cyclooxygenase-2; PG, prostaglandin; NO, nitric oxide; FSH, follicle-stimulating hormone.

localized by *in situ* hybridization in granulosa and cumulus cells from rat antral follicles (Kol *et al.* 1999c). With this technique, IL-1ra mRNA has never been detected in primordial follicles, whereas it was abundantly expressed in granulosa and theca cells from growing follicles (Wang *et al.* 1997). IL-1ra has been detected by RT-PCR in human (De Los Santos *et al.* 1998) and equine (Martoriati *et al.* 2002) cumulus cells. IL-1ra mRNA has been also demonstrated in equine granulosa cells, and its quantity varies during preovulatory maturation (Martoriati & Gérard 2003).

#### *IL-1R1 and IL-1R2*

IL-1R1 was first detected in human granulosa and theca cells (Hurwitz *et al.* 1992). IL-1R1 mRNA is expressed neither by the human oocyte (De Los Santos *et al.* 1998) nor by the equine oocyte (Martoriati *et al.* 2002), but it is present in cumulus cells of both species (De Los Santos *et al.* 1998, Martoriati *et al.* 2002), and in human embryos (De Los Santos *et al.* 1998). The expression sites of IL-1R1 vary with follicular development in the mouse. IL-1R1 mRNA is synthesized by theca cells from growing follicles. Before ovulation, IL-1R1 mRNA is expressed by cumulus and granulosa cells. It is abundantly expressed in the mouse oocyte all along follicular development (Simon *et al.* 1994), contrary to the human oocyte. In the rat, data concerning IL-1R1 ovarian localization are contradictory. IL-1R1 mRNA has been localized by *in situ* hybridization in the granulosa and theca cells of immature ovaries, and in the oocyte at the time of ovulation (Kol *et al.* 1999a). Scherzer *et al.* (1996) have also shown the presence of IL-1R1 in granulosa cells from immature rats, whereas

Wang *et al.* (1997) have demonstrated that IL-1R1 mRNA is present in granulosa and theca cells from growing follicles but absent from primordial and preantral follicles. Moreover, in rat preovulatory follicles, IL-1R1 mRNA is more abundant in theca cells than in granulosa cells (Wang *et al.* 1997), leading to the hypothesis that in the rat IL-1 acts on granulosa cells during follicular development and on theca cells at the time of ovulation.

IL-1R2 has not been much studied. IL-1R2 mRNA has not been detected in the ovary of immature rats (Kol *et al.* 1999a), but has been demonstrated in cultured ovarian cells. We showed recently by RT-PCR that IL-1R2 mRNA is synthesized in equine cumulus cells and oocytes, before and after *in vitro* maturation (Martoriati *et al.* 2002). Moreover, in contrast to IL-1R1, IL-1R2 mRNA is expressed in equine granulosa cells, but its level does not vary significantly during final follicular maturation (Martoriati & Gérard 2003).

#### **Roles of the IL-1 system in the ovary**

During the inflammatory process, numerous mechanisms are activated against infection, such as synthesis of proteolytic enzymes and production of PGs and nitric oxide (NO). Pro-inflammatory cytokines in general, and IL-1 in particular, are initiatory and regulatory factors of these mechanisms. Some of them are observed in the ovary during the periovulatory period. IL-1 has thus been hypothesized to be involved in the ovulatory process, as well as in some ovarian function such as steroidogenesis. The functions discussed below are summarized in Fig. 2.



### Roles of IL-1 in ovulation and in oocyte maturation

Several studies have demonstrated directly or indirectly that IL-1 may intervene in oocyte maturation and ovulation. In *ex vivo* perfused ovaries used as model, IL-1 $\beta$  induces ovulation (in the rat: Brännström *et al.* 1993a, Van der Hoek *et al.* 1998; in the rabbit: Takehara *et al.* 1994) similarly to LH or hCG. In the rat, IL-1 $\beta$  potentiates the inductive ovulatory effect of LH by increasing the rate of ovulated oocytes (Brännström *et al.* 1993a). In the mare, the intrafollicular injection of IL-1 $\beta$  at the pre-ovulatory stage mimics the effect of an i.v. injection of gonadotropins by inducing ovulation (Martoriati *et al.* 2003). In contrast, the use of IL-1ra in the perfusion medium (Peterson *et al.* 1993), by intraovarian injection (Simon *et al.* 1994), or by intrafollicular injection (Martoriati *et al.* 2003) reduces the ovulation rate or delays the ovulation time. These studies have confirmed that IL-1 is involved in ovulation, and that this effect is mediated by a specific receptor.

There are not many results on the oocyte–cumulus complex and they are contradictory. In the rat, the ovarian perfusion model allowed the demonstration that IL-1 $\beta$  has no effect on meiosis resumption of oocytes (Brännström *et al.* 1993a). In the rat, the intraovarian injection of IL-1ra decreases the expansion rate of cumulus cells (Simon *et al.* 1994), which may explain the decreased ovulation rate observed. In the rabbit, IL-1 $\beta$  ovarian perfusion induces oocyte meiosis resumption and ovulation (Takehara *et al.* 1994). Recently in the mare, we demonstrated that the intrafollicular injection of IL-1 $\beta$  increases the oocyte maturation rate (Martoriati *et al.* 2003). The effect of IL-1 $\beta$  on oocytes could be mediated via cumulus cells.

Taken together, these results highlight that the effects of IL-1 $\beta$  on oocyte maturation are contradictory and may be species-dependent.

### Role of IL-1 in inflammatory-linked mechanisms in the ovary

#### Production and activation of proteolytic enzymes

Hurwitz *et al.* (1993) have demonstrated that *in vitro* treatment of rat ovarian cells with IL-1 $\beta$  leads to the accumulation in the culture medium of a 92 kDa gelatinase. Its expression is IL-1 $\beta$  dose-dependent and inhibited by IL-1ra. This gelatinase could be involved in the ovulatory process. In contrast, IL-1 $\beta$  inhibits plasminogen activator activity in cultured preovulatory follicles (Bonello *et al.* 1995). IL-1 $\beta$  acts predominantly by activating some plasminogen activator inhibitors (Hurwitz *et al.* 1994, Piquette *et al.* 1994, Karakji & Tsang 1995).

**PG production** PGs are important factors involved in the ovulatory process, since injection of inhibitors blocks ovulation (Wallach *et al.* 1975, Ainsworth *et al.* 1979, Watson & Sertich 1991, Brännström 1993). The ovarian production of PGs and its regulation has been studied by several authors. Their results lead us to conclude that IL-1

intervenes in PG production, mainly by acting on cyclooxygenase-2 (COX-2) synthesis. Actually, IL-1 $\beta$  induces *in vitro* PGE2 and PGF2 $\alpha$  production by granulosa cells (humans: Watanabe *et al.* 1993; rats: Hurwitz *et al.* 1995; cattle: Acosta *et al.* 1998). Moreover, it has been demonstrated *in vitro* that IL-1 $\beta$  induces an increase in 6 keto-PGF1 $\alpha$ , PGE2 and PGF2 $\alpha$  in cultured rat pre-ovulatory follicles (Brännström *et al.* 1993b) and bovine granulosa cells (Nothnick & Pate 1990). This effect may be triggered by sphingomyelin hydrolysis and ceramide production (Santana *et al.* 1996). Finally, *in vivo* IL-1 $\beta$  concentration in human follicular fluid is correlated with PGE2 and PGF2 $\alpha$  concentrations (Watanabe *et al.* 1994). By using an ovarian perfusion model, Peterson *et al.* (1993) confirmed these observations in the rat. More precisely, the mechanisms by which IL-1 $\beta$  regulates PG production and action have been studied. Narko *et al.* (1997) demonstrated that IL-1 $\beta$  induces *in vitro* COX-2 mRNA synthesis in human granulosa–luteal cells. This has been confirmed in rat granulosa cells (Ando *et al.* 1999) and mouse cumulus cells (Joyce *et al.* 2001). Narko *et al.* (2001) have shown that IL-1 $\beta$  induces PGF2 $\alpha$  receptor mRNA synthesis as well as EP2 and EP4 (two PGE2 receptor sub-types) mRNA synthesis in human granulosa cells.

IL-1 also induces an increase in A2 phospholipase activity (Townson & Pate 1994, Kol *et al.* 1997), induces the synthesis of PGS2 (Narko *et al.* 1997, Ando *et al.* 1998) and stabilizes its mRNA (Saito *et al.* 2001). This effect may be triggered by ceramides (Irahara *et al.* 1999). Interestingly, Davis *et al.* (1999) demonstrated that IL-1 $\beta$  is able to restore ovulation in mice carrying a null mutation for COX-2, and which thus fail to ovulate.

**NO production** Ahsan *et al.* (1997) have shown that IL-1 can induce NO production in the ovary. In humans, Tao *et al.* (1997) have demonstrated that follicular cells incubated 24 h in the presence of IL-1 $\beta$  show an increased ability to produce NO. IL-1 $\beta$  is able to inhibit apoptosis in rat ovarian follicles, by increasing NO production (Chun *et al.* 1995). Addition of IL-1ra blocks these effects, leading to the hypothesis that IL-1 $\beta$  acts via a specific receptor. A study performed by Ben-Shlomo *et al.* (1994) showed that cell communications between granulosa and theca cells play a central role in NO ovarian production.

**Cellular metabolism** During terminal follicular maturation, the energy metabolism is profoundly changed (Billig *et al.* 1983). IL-1 $\beta$  increases lactate accumulation in cultured rat ovarian cells, and glucose consumption and transport in a time-, dose- and receptor-dependent manner. Granulosa–theca interactions are essential (Ben-Shlomo *et al.* 1997).

**Steroidogenesis** Numerous studies have focused on the effect of IL-1 on steroidogenesis. *In vitro* studies have demonstrated that IL-1 $\beta$  inhibits granulosa cell

progesterone production in various species (rat: Gottschall *et al.* 1987, 1988, Kasson & Gorospe 1989, Brännström *et al.* 1993b; pig: Fukuoka *et al.* 1989; rabbit: Bréard *et al.* 1998). On the contrary, progesterone production by granulosa cells is increased *in vitro* by IL-1 $\beta$  in cattle (Baratta *et al.* 1996), and by IL-1 $\alpha$  in humans (Sjogren *et al.* 1991), as well as in hamster preovulatory follicles (Nakamura *et al.* 1990). This effect may be triggered by sphingomyelin hydrolysis and ceramide production (Santana *et al.* 1996). Other studies have demonstrated no obvious effect of IL-1 $\beta$  on progesterone production (cattle: Nothnick & Pate 1990, Acosta *et al.* 1998; woman: Barak *et al.* 1992). Furthermore, IL-1 may have some effect on estradiol-17 $\beta$  production. It has been shown *in vitro* in human granulosa cells that IL-1 $\beta$  inhibits estradiol-17 $\beta$  production (Barak *et al.* 1992), most probably by increasing NO production (Tobai & Nishiya 2001). IL-1 could also inhibit P450 aromatase activity (Yasuda *et al.* 1990, Ghersevich *et al.* 2001) as well as other enzymes involved in estradiol-17 $\beta$  synthesis (Hurwitz *et al.* 1991, Ghersevich *et al.* 2001). A similar result was observed in cattle (Baratta *et al.* 1996). In rat granulosa cells, Gottschall *et al.* (1989) and Zhou & Galway (1991) have demonstrated a dose-dependent inhibition of IL-1 $\beta$  on the follicle-stimulating hormone (FSH) estrogen production. The effect of IL-1 $\beta$  on FSH receptor can be hypothesized, since in the rat ovary IL-1 $\beta$  decreases the quantity of gonadotropin receptors (Gottschall *et al.* 1987, 1988, Kasson & Gorospe 1989).

## Conclusions

The data reviewed above provide substantial evidence for the existence of a local ovarian IL-1 system. Despite the apparent preliminary nature of the observations, there is every reason to believe that IL-1 play a major role throughout the ovarian life cycle, in particular in the ovulatory process. Future investigations will most likely reveal important data relevant to the pathways of IL-1 production, regulation and actions. These will help toward a fuller understanding of IL-1 involvement in the ovarian function and female fertility.

## Acknowledgements

The authors are grateful to Ms A Lacombe (Equipe Traduction, INRA, Jouy en Josas, France) for proof reading and correction of the English.

## Funding

The work was supported by grants from the Haras Nationaux (France). M C and A M are supported by

fellowships from Haras Nationaux (France), INRA (France) and Région Centre (France). Authors declare that there is no conflict of interest that would prejudice impartiality.

## References

- Acosta TJ, Miyamoto A, Ozawa T, Wijayagunawardane MP & Sato K 1998 Local release of steroid hormones, prostaglandin E<sub>2</sub>, and endothelin-1 from bovine mature follicles *in vitro*: effects of luteinizing hormone, endothelin-1, and cytokines. *Biology of Reproduction* **59** 437–443.
- Ahsan S, Lacey M & Whitehead SA 1997 Interactions between interleukin-1 beta, nitric oxide and prostaglandin E<sub>2</sub> in the rat ovary: effects on steroidogenesis. *European Journal of Endocrinology* **137** 293–300.
- Ainsworth L, Tsang BK, Downey BR, Baker RD, Marcus GJ & Armstrong DT 1979 Effects of indomethacin on ovulation and luteal function in gilts. *Biology of Reproduction* **31** 115–121.
- Ando M, Kol S, Kokia E, Ruutuinen-Altman K, Sirois J, Rohan RM, Payne DW & Adashi EY 1998 Rat ovarian prostaglandin endoperoxide synthase-1 and -2: periovulatory expression of granulosa cell-based interleukin-1-dependent enzymes. *Endocrinology* **139** 2501–2508.
- Ando M, Kol S, Irahara M, Sirois J & Adashi EY 1999 Non-steroidal anti-inflammatory drugs (NSAIDs) block the late, prostanoid-dependent/ceramide-independent component of ovarian IL-1 action: implications for the ovulatory process. *Molecular and Cellular Endocrinology* **157** 21–30.
- Arend WP & Guthridge CJ 2000 Biological role of interleukin 1 receptor antagonist isoforms. *Annals of the Rheumatic Diseases* **59** 160–164.
- Bailly S, Ferrua B, Fay M & Gougerot-Pocidal MA 1990 Paraformaldehyde fixation of LPS-stimulated human monocytes: technical parameters permitting the study of membrane IL-1 activity. *European Cytokine Network* **1** 47–51.
- Barak V, Yanai P, Trevers AJ, Roisman I, Simon A & Laufer N 1992 Interleukin-1: local production and modulation of human granulosa luteal cells steroidogenesis. *Fertility and Sterility* **58** 719–725.
- Baratta M, Basini G, Bussolati S & Tamanini C 1996 Effects of interleukin-1 beta fragment (163–171) on progesterone and estradiol-17 beta release by bovine granulosa cells from different size follicles. *Regulatory Peptides* **67** 187–194.
- Ben-Shlomo I & Adashi EY 1994 Interleukin-1 as a mediator of the ovulatory sequence: evidence for a meaningful role of cytokines in ovarian physiology. *Current Science* **1** 187–192.
- Ben-Shlomo I, Kokia E, Jackson MJ, Adashi EY & Payne DW 1994 Interleukin-1 beta stimulates nitrite production in the rat ovary: evidence for heterologous cell-cell interaction and for insulin-mediated regulation of the inducible isoform of nitric oxide synthase. *Biology of Reproduction* **51** 310–318.
- Ben-Shlomo I, Kol S, Roeder LM, Resnick CE, Hurwitz A, Payne DW & Adashi EY 1997 Interleukin (IL)-1 beta increases glucose uptake and induces glycolysis in aerobically cultured rat ovarian cells: evidence that IL-1 beta may mediate the gonadotropin-induced midcycle metabolic shift. *Endocrinology* **138** 2680–2688.
- Billig H, Hedin L & Magnusson C 1983 Gonadotrophins stimulate lactate production by rat cumulus and granulosa cells. *Acta Endocrinologica* **103** 562–566.
- Bonello NP, Norman RJ & Brännström M 1995 Interleukin-1 $\beta$  inhibits luteinizing hormone-induced plasminogen activator activity in rat preovulatory follicles *in vitro*. *Endocrine* **3** 49–54.
- Brännström M 1993 Inhibitory effect of mifepristone (RU 486) on ovulation in the isolated perfused rat ovary. *Contraception* **48** 393–402.

- Brännström M, Wang L & Norman RJ 1993a Ovarian effect of interleukin-1 $\beta$  on the perfused rat ovary. *Endocrinology* **132** 399–404.
- Brännström M, Wang L & Norman RJ 1993b Effects of cytokines on prostaglandin production and steroidogenesis of incubated preovulatory follicles of the rat. *Biology of Reproduction* **48** 165–171.
- Brännström M, Norman RJ, Seamark RF & Robertson SA 1994 Rat ovary produces cytokines during ovulation. *Biology of Reproduction* **50** 88–94.
- Bréard E, Delarue B, Benhaim A, Feral C & Leymarie P 1998 Inhibition by rabbit granulosa and theca cells: effects on gonadotropin-induced progesterone production. *European Journal of Endocrinology* **138** 328–336.
- Butcher C, Steinkasserer A, Tejura S & Lennard AC 1994 Comparison of two promoters controlling expression of secreted or intracellular IL-1 receptor antagonist. *Journal of Immunology* **153** 701–711.
- Carberg M, Nejaty J, Frøysa B, Guan Y, Söder O & Bergqvist A 2000 Elevated expression of tumor necrosis factor  $\alpha$  in cultured granulosa cells from women with endometriosis. *Human Reproduction* **15** 1250–1255.
- Carter DB, Deibel MR Jr, Dunn CJ, Tomich CS, Laborde AL, Slightom JL, Berger AE, Bienkowski MJ, Sun FF, McEwan RN *et al.* 1990 Purification, cloning, expression and biological characterization of an interleukin-1 receptor antagonist protein. *Nature* **344** 633–638.
- Cavaillon JM 1991 Interleukine-1. In *Les Cytokines*, ch 14, pp 145–166. Eds Masson SA. Paris.
- Chun SY, Eisenhauer KM, Kubo M & Hsueh AJW 1995 Interleukin-1 $\beta$  suppresses apoptosis in rat ovarian follicles by increasing nitric oxide production. *Endocrinology* **136** 3120–3127.
- Colotta F, Dower SK, Sims JE & Mantovani A 1994 The type II 'decoy' receptor: a novel regulatory pathway for interleukin 1. *Immunology Today* **15** 562–566.
- Davis B, Lennard DE, Lee CA, Tiano HF, Morham SG, Wetsel WC & Langenbac R 1999 Anovulation in cyclooxygenase-2-deficient mice is restored by prostaglandin E2 and interleukin-1 $\beta$ . *Endocrinology* **140** 2685–2695.
- De Los Santos MJ, Mercader A, Frances A, Portoles E, Remohi J, Pellicer A & Simon C 1996 Role of endometrial factors in regulating secretion of components of the immunoreactive human embryonic interleukin-1 system during embryonic development. *Biology of Reproduction* **54** 563–574.
- De Los Santos MJ, Anderson DJ, Racowsky C, Simon C & Hill JA 1998 Expression of interleukin-1 system genes in human gametes. *Biology of Reproduction* **59** 1419–1424.
- Dinarello CA 1991 Interleukin-1. In *The Cytokine Handbook*, ch 3, pp 47–82. Ed. Thomson AW. New-York: Academic Press.
- Dower SK, Kronheim SR, March CJ, Conlon PJ, Hopp TP, Gillis S & Urdal DL 1985 Detection and characterization of high affinity plasma membrane receptors for human interleukin 1. *Journal of Experimental Medicine* **162** 501–515.
- Dower SK, Kronheim SR, Hopp TP, Cantrell M, Deeley M, Gillis S, Henney CS & Urdal DL 1986 The cell surface receptor for interleukin-1 alpha and interleukin-1 beta are identical. *Nature* **324** 266–268.
- Dower SK, Sims JE, Stanton TH, Slack J, McMahan CJ, Valentine MA & Bomsztyk K 1990 Molecular heterogeneity of interleukin-1 receptors. *Annals of the New York Academy of Sciences* **594** 231–239.
- Eisenberg SP, Evans RJ, Arend WP, Verderber E, Brewer MT, Hannum CH & Thompson RC 1990 Primary structure and functional expression from complementary DNA of a human interleukin-1 receptor antagonist. *Nature* **343** 341–346.
- Eisenberg SP, Brewer MT, Verderber E, Heindal P, Brandhuber BJ & Thompson RC 1991 Interleukin-1 receptor antagonist is a member of the interleukin 1 gene family: evolution of a cytokine control mechanism. *PNAS* **88** 5232–5236.
- Fantuzzi G 2001 Lessons from interleukin-deficient mice: the interleukin-1 system. *Acta Physiologica Scandinavica* **173** 5–9.
- Fukuoka M, Yasuda K, Taii S, Takakura K & Mori T 1989 Interleukin-1 stimulates growth and inhibits progesterone secretion in cultured of porcine granulosa cells. *Endocrinology* **124** 884–890.
- Furutani Y, Notake M, Yamayoshi M, Nomura H, Ohue M, Furuta R, Fukui T, Yamada M & Nakamura S 1985 Cloning and characterization of the cDNAs for human and rabbit interleukin-1 precursor. *Nucleic Acids Research* **13** 5869–5882.
- Gabellec MM, Griffais R, Fillion G & Haour F 1996 Interleukin-1 receptors type I and type II in the mouse brain: kinetics of mRNA expressions after peripheral administration of bacterial lipopolysaccharide. *Journal of Neuroimmunology* **66** 65–70.
- Géry I & Waksman BH 1972 Potentiation of the T-lymphocyte response to mitogens. II. The cellular source of potentiating mediator(s). *Journal of Experimental Medicine* **136** 143–155.
- Ghersevich S, Isomaa V & Vihko P 2001 Cytokine regulation of the expression of estrogenic biosynthetic enzymes in cultured rat granulosa cells. *Molecular and Cellular Endocrinology* **172** 21–30.
- Giulan D, Young DG, Woodward J, Brown DC & Lachman LB 1988 Interleukin-1 is an astroglial growth factor in the developing brain. *Journal of Neurosciences* **8** 709–714.
- Gottschall PE, Uehara A, Talbot Hoffmann S & Arimura A 1987 Interleukin-1 inhibits follicle stimulating hormone-induced differentiation in rat granulosa cells *in vitro*. *Biochemical and Biophysical Research Communications* **149** 502–509.
- Gottschall PE, Katsuura G, Dahl RR, Hoffmann ST & Arimura A 1988 Discordance in the effects of interleukin-1 on rat granulosa cell differentiation induced by follicle-stimulating hormone or activators of adenylate cyclase. *Biology of Reproduction* **39** 1074–1085.
- Gottschall PE, Katsuura G & Arimura A 1989 Interleukin-1 suppresses follicle-stimulating hormone-induced estradiol secretion from cultured ovarian granulosa cells. *Journal of Reproduction and Immunology* **15** 281–290.
- Granhölm T & Söder C 1991 Constitutive production of lymphocyte activating factors by normal tissues in the adult rat. *Journal of Cellular Biochemistry* **46** 143–151.
- Granowitz EV, Santos AA, Poutsika DD, Cannon JG, Wilmore DW, Wolf SM & Dinarello CA 1991 Production of interleukin-1-receptor antagonist during experimental endotoxaemia. *Lancet* **338** 1423–1424.
- Gray PW, Glaiser D, Chen E, Goeddel DV & Pennica D 1986 Two interleukin-1 genes in the mouse: cloning and expression of the cDNA for murine interleukin-1 $\beta$ . *Journal of Immunology* **137** 3644–3648.
- Hannum CH, Wilcox CJ, Arend WP, Joslin FG, Dripps DJ, Heimdal PL, Armes LG, Sommer A, Eisenberg SP & Thompson RC 1990 Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. *Nature* **343** 336–340.
- Haskill S, Martin G, Van Le L, Morris J, Peace A, Bigler CF, Jaffe GJ, Hammerberg C, Sporn SA, Fong S *et al.* 1991 cDNA cloning of an intracellular form of the human interleukin 1 receptor antagonist associated with epithelium. *PNAS* **88** 3681–3685.
- Howard RD, McIlwraith CW, Trotter GW & Nyberg JK 1998 Cloning of equine interleukin-1 alpha and equine interleukin-1 beta and determination of their full-length cDNA sequences. *American Journal of Veterinary Research* **59** 704–711.
- Hurwitz A, Payne DW, Packman JN, Andreani CL, Resnick CE, Hernandez ER & Adashi EY 1991 Cytokine-mediated regulation of ovarian function: interleukin-1 inhibits gonadotropin-induced androgen bio-synthesis. *Endocrinology* **129** 1250–1256.
- Hurwitz A, Loukides J, Rissiarelli E, Botero L, Katz E, McAllister JM, Garcia JE, Rohan R, Adashi EY & Hernandez ER 1992 Human intraovarian interleukin-1 (IL-1) system: highly compartmentalized and hormonally dependent regulation of the genes encoding IL-1, its receptor, and its receptor antagonist. *Journal of Clinical Investigation* **89** 1746–1754.



- Hurwitz A, Dushnik M, Solomon H, Ben-Chetrit A, Finci-Yeheskel Z, Milwidsky A, Mayer M, Adashi EY & Yagel S 1993 Cytokine-mediated regulation of rat ovarian function: interleukin-1 stimulates the accumulation of a 92-kilodalton gelatinase. *Endocrinology* **132** 2709–2714.
- Hurwitz A, Finci-Yeheskel Z, Dushnik M, Milwidsky A, Ben-Chetrit A, Yagel S, Adashi EY & Mayer M 1994 Cytokine-mediated regulation of rat ovarian function: interleukin-1 inhibits plasminogen activator activity through the induction of plasminogen activator inhibitor-1 (PAI-1). *Molecular and Cellular Endocrinology* **101** 307–314.
- Hurwitz A, Finci-Yeheskel Z, Dushnik M, Milwidsky A, Shimonovitz S, Yagel S, Adashi EY & Mayer M 1995 Interleukin-1-mediated regulation of plasminogen activation in pregnant mare serum gonadotropin-primed rat granulosa cells is independent of prostaglandin production. *Journal of the Society for Gynecologic Investigation* **2** 691–699.
- Irahara M, Ando M, Sirois J, Saito J & Adashi EY 1999 Glucocorticoid receptor-mediated post-ceramide inhibition of interleukin-1 $\beta$ -dependent induction of ovarian prostaglandin endoperoxide synthase-2 in rats. *Biology of Reproduction* **60** 946–953.
- Jasper M & Norman RJ 1995 Immunoactive interleukin-1 beta and tumour necrosis factor-alpha in thecal, stromal and granulosa cell cultures from normal and polycystic ovaries. *Human Reproduction* **10** 1352–1354.
- Joyce IM, Pendola FL, O'Brien M & Eppig JJ 2001 Regulation of prostaglandin-endoperoxide synthase 2 messenger ribonucleic acid expression in mouse granulosa cells during ovulation. *Endocrinology* **142** 3187–3197.
- Karagouni EE, Chryssikopoulos A, Mantzavinos T, Kanakas N & Dotsika EN 1998 Interleukin-1 beta and interleukin-1 alpha may affect the implantation rate of patients undergoing *in vitro* fertilization-embryo transfer. *Fertility and Sterility* **70** 553–559.
- Karakji EG & Tsang BK 1995 Regulation of rat granulosa cell plasminogen activator system: influence of interleukin-1 $\beta$  and ovarian follicular development. *Biology of Reproduction* **53** 1302–1310.
- Kasson BG & Gorospe WC 1989 Effects of interleukins 1, 2 and 3 on follicle-stimulating hormone-induced differentiation of rat granulosa cells. *Molecular and Cellular Endocrinology* **62** 103–111.
- Khan SA, Söder O, Syed V, Gustafsson K, Lindh M & Ritzén EM 1987 The rat testis produces large amounts of an interleukin-1-like factor. *International Journal of Andrology* **10** 495–503.
- Khan SA, Schmidt K, Hallin P, Di Pauli R, Geyter CH & Nieschlag E 1988 Human testis cytosol and ovarian follicular fluid contain high amounts of interleukin-1 like factor(s). *Molecular and Cellular Endocrinology* **58** 221–230.
- Kilian PL, Kaffka KL, Stern AS, Woehle D, Benjamin WR, Dechiara TM, Gubler U, Farrar JJ, Mizel SB & Lomedico PT 1986 Interleukin-1 alpha and interleukin-1 beta bind to the same receptor on T cells. *Journal of Immunology* **136** 4509–4514.
- Kol S, Ben-Shlomo I, Ando M, Payne DW & Adashi EY 1997 Interleukin-1 beta stimulates ovarian phospholipase A2 (PLA2) expression and activity: up-regulation of both secretory and cytosolic PLA2. *Endocrinology* **138** 314–321.
- Kol S, Donesky BW, Ruutiainen-Altman K, Ben-Shlomo I, Irahara M, Ando M, Rohan RM & Adashi EY 1999a Ovarian interleukin-1 receptor antagonist in rats: gene expression, cellular localization, cyclic variation, and hormonal regulation of a potential determinant of interleukin-1 action. *Biology of Reproduction* **61** 274–282.
- Kol S, Ruutiainen-Altman K, Scherzer WJ, Ben-Shlomo I, Ando M, Rohan RM & Adashi EY 1999b The rat intraovarian interleukin (IL)-1 system: cellular localization, cyclic variation and hormonal regulation of IL-1 $\beta$  and of the type I and type II IL-1 receptors. *Molecular and Cellular Endocrinology* **149** 115–128.
- Kol S, Wong KH, Ando M, Ben-Shlomo I & Adashi EY 1999c Rat ovarian interleukin-1 alpha: interleukin-1-dependent *in vitro* expression. *Endocrine* **11** 269–275.
- Kurt-Jones EA, Beller DI, Mizel SB & Unanue ER 1985 Identification of a membrane-associated interleukin 1 in macrophages. *PNAS* **82** 1204–1208.
- Lomedico PT, Gubler U, Hellmann CP, Dukovich M, Giri JG, Pan YC, Collier K, Semionov R, Chua AO & Mizel SB 1984 Cloning and expression of murine interleukin-1 cDNA in *Escherichia coli*. *Nature* **312** 458–462.
- Luger TA, Stadler BM, Katz SI & Oppenheim JJ 1981 Epidermal cell (keratinocyte) derived thymocyte activating factor (ETAF). *Journal of Immunology* **127** 1493–1498.
- Machelon V & Emilie D 1997 Production of ovarian cytokines and their role in ovulation in the mammalian ovary. *European Cytokine Network* **8** 137–143.
- MacMahan CJ, Slack JL, Mosley B, Cosman D, Lupton SD, Brunton LL, Grubin CE, Wignall JM, Jenkins NA, Brannan CI *et al.* 1991 A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. *EMBO Journal* **10** 2821–2832.
- March CJ, Mosley B, Larsen A, Cerretti DP, Braedt G, Price V, Gillis S, Henney CS, Kronheim SR, Grabstein K *et al.* 1985 Cloning, sequence and expression of two distinct human interleukin-1 complementary DNAs. *Nature* **315** 641–647.
- Martin U & Falk W 1997 The interleukin-1 receptor complex and interleukin-1 signal transduction. *European Cytokine Network* **8** 5–17.
- Martin U & Resch 1988 Interleukin 1: more than a mediator between leukocytes. *Trends in Pharmacological Sciences* **9** 171–177.
- Martoriati A & Gérard N 2003 Interleukin-1 (IL-1) system gene expression in granulosa cells: kinetics during terminal preovulatory follicle maturation in the mare. *Reproductive Biology and Endocrinology* **1** 42–52.
- Martoriati A, Lalmanach A-C, Goudet G & Gérard N 2002 Expression of interleukin-1 (IL-1) system genes in equine cumulus-oocyte complexes and influence of IL-1 $\beta$  during *in vitro* maturation. *Biology of Reproduction* **67** 630–636.
- Martoriati A, Duchamp G & Gérard N 2003 *In vivo* effect of epidermal growth factor (EGF), interleukin-1 $\beta$  (IL-1 $\beta$ ) and interleukin-1RA (IL-1RA) on equine preovulatory follicles. *Biology of Reproduction* **68** 1748–1754.
- Matsushima K, Akahoshi T, Yamada M, Furutani Y & Oppenheim JJ 1986 Properties of a specific interleukin 1 (IL-1) receptor on human Epstein-Barr virus transformed B lymphocytes. Identity of the receptor for IL-1 $\alpha$  and IL-1 $\beta$ . *Journal of Immunology* **136** 4496–4502.
- Mendoza C, Cremades N, Ruiz-Requena E, Martínez F, Ortega E, Bernabeu S & Tesarik J 1999 Relationship between fertilization results after intracytoplasmic sperm injection, and intrafollicular steroid, pituitary hormone and cytokine concentrations. *Human Reproduction* **14** 628–635.
- Minnich-Carruth LL, Suttles J & Mizel SB 1989 Evidence against the existence of a membrane form of murine IL-1 $\alpha$ . *Journal of Immunology* **142** 526–530.
- Mori S, Goto F, Ohkawara S, Maeda S, Shimadda K & Yoshinaga M 1988 Cloning and sequence analysis of a cDNA for lymphocyte proliferation potentiating factor of rabbit polymorphonuclear leukocytes: identification rabbit interleukin-1 beta. *Biochemical and Biophysical Research Communications* **150** 1237–1243.
- Nakamura Y, Kato H & Terranova PF 1990 Interleukin-1 $\alpha$  increases thecal progesterone production of preovulatory follicles in cyclic hamsters. *Biology of Reproduction* **43** 169–173.
- Narko K, Ritvos O & Ristimäki A 1997 Induction of cyclooxygenase-2 and prostaglandin F2 alpha receptor expression by interleukin-1 beta in cultured human granulosa-luteal cells. *Endocrinology* **138** 3638–3644.
- Narko K, Saukkonen K, Ketola I, Bützow R, Heikinheimo M & Ristimäki A 2001 Regulated expression of prostaglandin E2 receptors EP2 and EP4 in human ovarian granulosa-luteal cells. *Journal of Clinical Endocrinology and Metabolism* **86** 1765–1768.



- Nishida T, Hirato T, Nishino N, Mizuno K, Sekiguchi Y, Takano M, Kawai K, Nakai S & Hirai Y 1988 Cloning of the cDNA for rat interleukin-1 $\alpha$  and  $\beta$ . In *Monokines and Other Non-Lymphocytic Cytokines*, pp 73–78. Eds Powenda MC, Oppenheim JJ, Kluger MJ & Dinarello. New-York: Alan R. Liss Inc.
- Nothnick WB & Pate JL 1990 Interleukin-1 $\beta$  is a potent stimulator of prostaglandin synthesis in bovine luteal cells. *Biology of Reproduction* **43** 898–903.
- Oppenheim JJ, Kovacs EJ, Matsushima K & Durum SK 1986 There is more than one interleukin-1. *Immunology Today* **7** 45–56.
- Peterson CM, Hales HA, Hatasaka HH, Mitchell MD, Rittenhouse L & Jones KP 1993 Interleukin-1 $\beta$  (IL-1 $\beta$ ) modulates prostaglandin production and the natural IL-1 receptor antagonist inhibits ovulation in the optimally stimulated rat ovarian perfusion model. *Endocrinology* **133** 2301–2306.
- Piquette GN, Simon C, el Damasouri I, Frances A & Polan ML 1994 Gene regulation of interleukin-1 beta, interleukin-1 receptor type I, and plasminogen activator inhibitor-1 and -2 in human granulosa-luteal cells. *Fertility and Sterility* **62** 760–770.
- Ribardo DA, Crowe SE, Kuhl KR, Peterson JW & Chopra AK 2001 Prostaglandin levels in stimulated macrophages are controlled by phospholipase A2-activating protein and by activation of phospholipase C and D. *Journal of Biological Chemistry* **276** 5467–5475.
- Roux-Lombard P 1998 The interleukin-1 family. *European Cytokine Network* **9** 565–576.
- Rubartelli A, Cozzolino F, Talio M & Sitia R 1990 A novel secretory pathway for interleukin-1 $\beta$ , a protein lacking a signal sequence. *EMBO Journal* **9** 1503–1510.
- Saito J, Ando M, Sussman D, Negishi H, King G & Adashi EY 2001 Interleukin 1 upregulates ovarian prostaglandin endoperoxide synthase-2 expression: evidence for prostaglandin-dependent/ceramide-independent transcriptional stimulation and for message stabilization. *Biology of Reproduction* **65** 1759–1765.
- Santana P, Llanes L, Hernandez I, Gonzalez-Robayna I, Tabraue C, Gonzalez-Reyes J, Quintana J, Estevez F, Ruiz de Galarreta CM & Fanjul LF 1996 Interleukin-1 beta stimulates sphingomyelin hydrolysis in cultured granulosa cells: evidence for a regulatory role of ceramide on progesterone and prostaglandin biosynthesis. *Endocrinology* **137** 2480–2489.
- Scherzer WJ, Ruutinen-Altman KS, Putowski LT, Kol S, Adashi EY & Rohan RM 1996 Detection and *in vivo* hormonal regulation of rat ovarian type I and type II interleukin-1 receptor mRNAs: increased expression during the periovarial period. *Journal of the Society for Gynecologic Investigation* **3** 131–139.
- Seckinger P, Williamson K, Balavoine JF, Mach B, Mazzei G, Shaw A & Dayer JM 1987 A urine inhibitor of interleukin 1 activity affects both interleukin 1 alpha and 1 beta but not tumor necrosis factor alpha. *Journal of Immunology* **139** 1541–1545.
- Simon C, Frances A, Piquette G & Polan ML 1994 Immunohistochemical localization of the interleukin-1 system in the mouse ovary during follicular growth, ovulation and luteinization. *Biology of Reproduction* **50** 449–457.
- Sims JE, Gayle MA, Slack JL, Alderson MR, Bird TA, Giri JG, Colotta F, Re F, Mantovani A, Shanebeck K *et al.* 1993 Interleukin 1 signaling occurs exclusively via the type I receptor. *PNAS* **90** 6155–6159.
- Sims JE, Giri JG & Dower SK 1994 The two interleukin-1 receptors play different roles in IL-1 actions. *Clinical Immunology and Immunopathology* **72** 9–14.
- Sjogren A, Holmes PV & Hillensjo T 1991 Interleukin-1 alpha modulates luteinizing hormone stimulated cyclic AMP and progesterone release from human granulosa cells *in vitro*. *Human Reproduction* **6** 910–913.
- Slack J, McMahan CJ, Waugh S, Schooley K, Spriggs MK, Sims JE & Dower SK 1993 Independent binding of interleukin-1 alpha and interleukin-1 beta to type I and type II interleukin-1 receptors. *Journal of Biological Chemistry* **268** 2513–2524.
- Symons JA, Eastgate JA & Duff GW 1991 Purification and characterization of a novel soluble receptor for interleukin 1. *Journal of Experimental Medicine* **174** 1251–1254.
- Takacs L, Kovacs EJ, Smith MR, Young HA & Durum SK 1988 Detection of IL-1 alpha and IL-1 beta gene expression by *in situ* hybridization. Tissue localization of IL-1 mRNA in the normal C57BL/6 mouse. *Journal of Immunology* **141** 3081–3095.
- Takakura K, Taii S, Fukuoka M, Yasuda K, Tagaya Y, Yodoi J & Mori T 1989 Interleukin-2 receptor/p55(Tac)-inducing activity in porcine follicular fluids. *Endocrinology* **125** 618–623.
- Takehara Y, Dharmarajan AM, Faufinan G & Wallach EE 1994 Effect of interleukin-1 $\beta$  on ovulation in the *in vitro* perfused rabbit ovary. *Endocrinology* **134** 1788–1793.
- Tao M, Kodama H, Kagabu S, Fukuda J, Murata M, Shimizu Y, Hirano H & Tanaka T 1997 Possible contribution of follicular interleukin-1 $\beta$  to nitric oxide generation in human pre-ovulatory follicles. *Human Reproduction* **12** 2220–2225.
- Terranova PF & Montgomery Rice V 1997 Review: cytokine involvement in ovarian processes. *American Journal of Reproductive Immunology* **37** 50–63.
- Tobai H & Nishiyama I 2001 Nitric oxide mediates inhibitory effect of interleukin-1 beta on estrogen production in human granulosa-luteal cells. *Journal of Obstetrics and Gynaecology Research* **27** 53–59.
- Townson DH & Pate JL 1994 Regulation of prostaglandin synthesis by interleukin-1 beta in cultured bovine luteal cells. *Biology of Reproduction* **51** 480–485.
- Van der Hoek KH, Woodhouse CM, Brännström M & Norman RJ 1998 Effects of interleukin (IL)-6 on luteinizing hormone and IL-1 beta-induced ovulation and steroidogenesis in the rat ovary. *Biology of Reproduction* **58** 1266–1271.
- Vannier E, Miller LC & Dinarello CA 1992 Coordinated antiinflammatory effects of interleukin 4: interleukin 4 suppresses interleukin 1 production but up-regulates gene expression and synthesis of interleukin 1 receptor antagonist. *PNAS* **89** 4076–4080.
- Wallach EE, Bronson R, Hamada Y, Wright KH & Stevens VC 1975 Effectiveness of prostaglandin F2 alpha in restoration of HMG-HCG induced ovulation in indomethacin-treated rhesus monkeys. *Prostaglandins* **10** 129–138.
- Wang LJ & Norman RJ 1992 Concentrations of immunoreactive interleukin-1 and interleukin-2 in human preovulatory follicular fluid. *Human Reproduction* **7** 147–150.
- Wang LJ, Brannstrom M, Cui KH, Simula AP, Hart RP, Maddocks S & Norman RJ 1997 Localisation of mRNA for interleukin-1 receptor and interleukin-1 receptor antagonist in the rat ovary. *Journal of Endocrinology* **152** 7–11.
- Watanabe H, Nagai K, Yamaguchi M, Ikenoue T & Mori N 1993 Interleukin-1 beta stimulates prostaglandin E2 and F2 alpha synthesis in human ovarian granulosa cells in culture. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **49** 963–967.
- Watanabe H, Nagai K, Yamaguchi M, Ikenoue T & Mori N 1994 Concentration of interleukin-1 beta correlates with prostaglandin E2 and F2 alpha in human pre-ovulatory follicular fluid. *Human Reproduction* **9** 9–12.
- Watson ED & Sertich PL 1991 Concentrations of arachidonate metabolites, steroids and histamine in preovulatory horse follicles after administration of human chorionic gonadotrophin and the effect of intrafollicular injection of indomethacin. *Journal of Endocrinology* **129** 131–139.
- Yasuda K, Fukuoka M, Taii S, Takakura K & Mori T 1990 Inhibitory effects of interleukin-1 on follicle-stimulating hormone induction of

- aromatase activity, progesterone secretion, and functional luteinizing hormone receptors in cultures of porcine granulosa cells. *Biology of Reproduction* **43** 905–912.
- Zhou MH & Galway AB 1991 Inhibitory effect of interleukin-1 beta on follicle stimulating hormone (FSH) induced estrogen production by cultured rat granulosa cells. *Sheng Li Xue Bao* **43** 67–72.
- Zolti M, Ben-Rafael Z, Meirum R, Shemesh M, Bider D, Mashiach S & Apte RN 1991 Cytokine involvement in oocytes and early embryos. *Fertility and Sterility* **56** 265–272.

Received in final form 7 October 2003

Accepted 17 October 2003

Made available online as an

Accepted Preprint 22 October 2003