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Macrophage contributions to ovarian function

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Macrophages are multifunctional cells that play key roles in the immune response and are abundant throughout female reproductive tissues. Macrophages are identified in tissues by their expression of cell surface receptors and can execute diverse functional activities, including phagocytosis and degradation of foreign antigens, matrix dissolution and tissue remodelling, and production and secretion of cytokines, chemokines and growth factors. Their specific localization and variations in distribution in the ovary during different stages of the cycle, as well as their presence in peri-ovulatory human follicular fluid, suggest that macrophages play diverse roles in intra-ovarian events including folliculogenesis, tissue restructuring at ovulation and corpus luteum formation and regression. This review presents the existing evidence for the regulation of ovarian function by macrophages and macrophage-derived products, highlighting the implications of these cells in ovarian diseases, particularly polycystic ovary syndrome, endometriosis and premature ovarian failure.

Key words: cytokine/macrophage/ovary/ovulation/polycystic ovary syndrome

Introduction

Macrophages are ubiquitous immune cells that play key roles in both innate and acquired immunity. However, in addition to protecting the body from foreign organisms and antigens, they maintain homeostasis in many tissues through their cytokine production and remodelling capabilities. With regard to female reproduction, macrophages contribute to the regulation of the pituitary–gonadal axis and are found throughout female reproductive tissues including the ovary, uterus, oviduct and mammary gland. In the ovary, macrophages have been detected in fluctuating numbers at various stages of the menstrual cycle (Brannstrom *et al*., 1993a, 1994b), and have had many different functions ascribed to them. The purpose of this review is to present the existing evidence for the regulation of ovarian function by macrophages and macrophage-derived products, highlighting the implications of these cells in ovarian diseases.

General characteristics and functions of macrophages

Macrophages are immune cells derived from bone-marrow precursors, which when mature, enter the bloodstream as monocytes. The adhesion of immune cells to endothelial cells and their subsequent migration into tissue is a three-step process (Butcher, 1992). Initial tethering via interactions between selectins on leukocytes (L-selectin) and endothelial cells (E- and P-selectins) mediates the slow rolling of leukocytes on endothelial cells. Exposure to cytokines and chemokines during this time activates the monocytes and stimulates the production of cell surface β_2 integrins, such as Mac-1 and LFA-1. Interactions between these leukocyte integrins and endothelial cell adhesion molecules, particularly those in the ICAM family, mediate firm adhesion of the monocytes and enable their migration between endothelial cells into tissues. Within tissues, differentiation of monocytes into macrophages occurs in response to the surrounding microenvironmental context, which directs the acquisition of tissue-specific phenotypes. For example, the initial cytokine exposure received by infiltrating monocytes can determine the functional phenotype of the maturing macrophage (Erwig *et al*., 1998) while the structure of the extracellular matrix (ECM) *in vitro* can also modulate macrophage function (Newman and Tucci, 1990; Gudewicz *et al*., 1994).

Within most organs, macrophages are involved in tissue homeostasis via their ability to execute diverse functional activities, including (i) phagocytosis and degradation of foreign antigens, (ii) matrix dissolution and tissue remodelling, and (iii) production and secretion of growth factors, cytokines and chemokines (Gordon, 1999a). These effector functions allow the macrophage to regulate local immune and inflammatory responses as well as influence normal tissue function. Each of these major macrophage effector functions and the various phases of the ovarian cycle that they are thought to impact are shown

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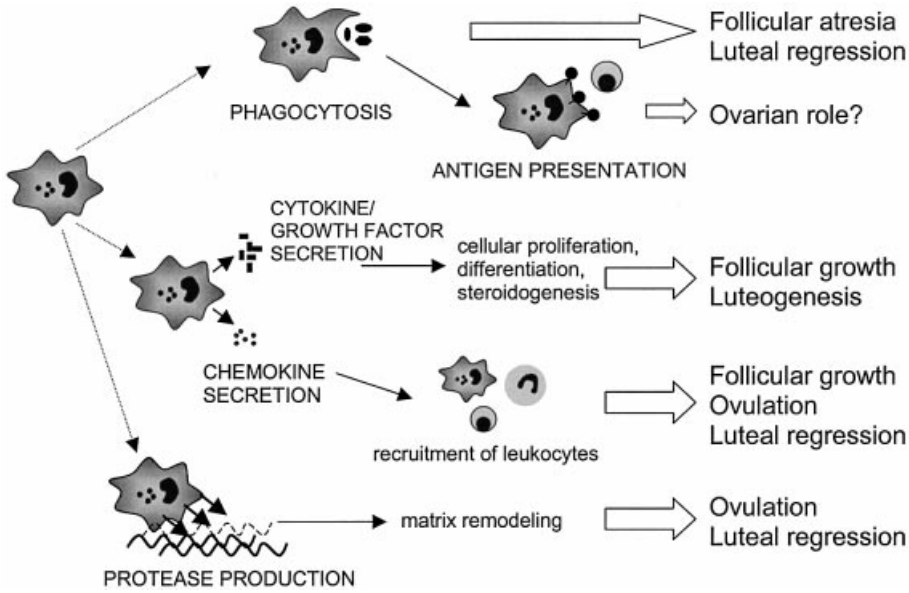

Figure 1. Macrophage involvement in ovarian function. As summarized in the text and cited references, macrophages: (1) are phagocytic and involved in the removal of apoptotic cellular debris; (2) present peptide antigens and activate T cells; (3) release cytokines and growth factors that are known to regulate many functional aspects of granulosa and theca cells; (4) release chemokines that attract and activate additional monocytes, neutrophils and T cells into the ovary from circulation; (5) secrete an array of proteases that degrade matrix as well as release/alter matrix- or membrane-bound proteins. Thus, the tissue specific localization and diverse functions of macrophages enable them to potentially impact multiple aspects of ovarian function.

Table I. Localization and function of macrophage-specific markers

Marker	Location	Understood functions
F4/80 (EMR-1)[a]	Pan murine macrophage marker	Cell–cell adhesion following adhesion to the extracellular matrix as well as some signalling capacity
Macrosialin (CD68)[a]	Predominantly intracellular in tissue macrophages.	Binds oxidized lipoprotein
Complement receptor 3 (CD11b/Mac-1)[a]	Transmembrane	Binds complement, participates in phagocytosis of particles, and mediates leukocyte migration out of vasculature
Class II MHC (Ia)[a]	Found on antigen-presenting macrophages, i.e. dendritic cells	Binds exogenously derived peptides for recognition by T cells
Fc receptors (CD16/CD32/CD23)	Transmembrane/soluble	Binds constant portion of IgG molecule initiating either transport of IgG across the epithelial cell surface or the initiation of an immune response
Mannose receptor (CD206)	Type I transmembrane molecule, found on mature tissue macrophages	Binds bacterial and fungal glycoproteins and mediates uptake during host defence
Scavenger receptors (CD204)	Transmembrane glycoprotein on mature tissue macrophages	Binds lipoproteins and participates in uptake of apoptotic cells and pathogens
Sialoadhesin (SER-4/3D6)	Transmembrane on stromal macrophages in bone marrow, and lymphoid organs	Adhesion molecule which mediates the binding but not uptake of attached cells
Lipopolysaccharide receptor (CD14)[a]	Glycosylphosphatidylinositol-linked plasma-membrane glycoprotein, on all macrophages	Binds bacterial lipopolysaccharide, triggers inflammatory responses

[a]Indicates markers which have been detected in the ovary. (Compiled from Austyn and Gordon, 1981; Ross *et al.*, 1985; Lachapelle et al., 1996; McKnight *et al.*, 1996; Daeron, 1997; Devitt *et al.*, 1998; McKnight and Gordon, 1998; Linehan *et al.*, 1999; Platt *et al.*, 1999.)

schematically in Figure 1 and will be described in greater detail below.

Identification of ovarian macrophages using macrophage-specific markers

Macrophages are identified in tissues by their expression of specific protein markers (Table I), which are predominantly cell surface receptors. The proteins considered most exclusively restricted to macrophages are F4/80 (the human homologue is EMR-1) and CD68 (also known as macrosialin in humans). F4/80, although its function is not fully understood, has been used extensively as a marker to identify macrophages in many tissues. In mouse ovaries, F4/80 positive cells exhibit marked changes in their distribution from neonatal to postpartum development

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(Li *et al*., 1998) and are found in the thecal, stromal (Van der Hoek *et al*., 2000) and luteal (Li *et al*., 1998) regions. CD68 is a well-established intracellular marker for macrophages, and has been widely used in immunohistochemical studies in both mouse (Van der Hoek *et al*., 2000) and human ovaries (Duncan *et al*., 1998; Gaytan *et al*., 1998a). CD68 positive cells are localized in human ovaries primarily to the vascular connective tissue and theca-lutein areas of the corpus luteum, although some are found in the granulosa-lutein cell layer (Gaytan *et al*., 1998b). Another widely used marker is class II MHC which is involved in antigen presentation by macrophages. Class II MHC positive macrophages have been identified in the ovary during the periovulatory period (Jasper *et al*., 2000), particularly in corpora lutea (Petrovska *et al*., 1992; Bukovsky *et al*., 1995; Lawler *et al*., 1999). Receptors that are involved in phagocytosis are also used as macrophage markers and include Fc receptors, complement receptors, mannose receptor, sialoadhesin, and scavenger receptors (reviewed by Aderem and Underhill, 1999; Gordon, 1999b). Among them, complement receptor 3 (Mac-1/CD11b) is involved in cell–cell and cell–matrix adhesion and CD11b positive cells have been shown in the mouse ovary within the theca layer and stroma immediately after ovulation and within the corpus luteum (Simon *et al*., 1994a; Tamura *et al*., 1998).

It is important to consider that the marker used to identify macrophages reveals specific information about the changing functional characteristics of the cells; for instance, in the rabbit, luteolysis was associated with an initial increase in scavenger receptor positive macrophages followed by recruitment of CD68 positive macrophages (Krusche *et al*., 2002). Table I highlights that multiple markers are used to identify macrophages in the ovary, as well as give insight into the various functions these macrophages may be exerting during the ovarian cycle.

Phagocytosis and antigen presentation

Macrophages are considered 'professional phagocytes' and can internalize particles much more rapidly and efficiently than other cells due to their expression of specific cell surface receptors (see Table I). Phagocytosis is a complex process involving recognition of an antigen by macrophage cell surface receptors, which initiates actin polymerization and internalization of the foreign molecule or organism into a phagosome (Allen and Aderem, 1996). Phagocytosis is followed by fusion of the phagosome with enzyme-containing lysosomes and degradation of the particle. Macrophages phagocytose endogenous and exogenous substances, such as cell debris, bacteria and viruses (Miller *et al*., 1983; Wei *et al*., 1988) and in culture will even phagocytose latex beads (Kirsch *et al*., 1981). When administration of exogenous particles was used to visualize phagocytosis, however, ovarian macrophages were reported to be less phagocytic than macrophages from other tissues (Itoh *et al*., 1999). Therefore ovarian macrophages may use phagocytosis primarily to remove apoptotic cells during specific phases of tissue remodelling as opposed to removal of foreign debris. Macrophages *in vivo* recognize and internalize apoptotic and necrotic cells, bringing about their efficient removal, and it has been shown that ovarian macrophages phagocytose atretic granulosa cells and apoptotic luteal cells in guinea-pigs, mice and humans (Paavola, 1979; Kuryszko and Adamski, 1987; Kasuya, 1997) thereby contributing to follicular atresia and luteolysis.

Following the phagocytosis of a foreign antigen, the macrophage is capable of intracellular degradation and presentation of the peptide fragments on the cell surface in association with the class II MHC. These class II MHC–antigen complexes are recognized by helper T cells via the T cell receptors CD3 and CD4. This results in the activation of both the T cell and the antigen-presenting macrophage and the initiation of a rapid immune response. Class II MHC-positive cells have been identified in the rat and human ovary (Hill *et al*., 1990; Bowen and Keyes, 2000) and equine corpora lutea (Lawler *et al*., 1999). In the human corpus luteum, abundant class II MHC positive cells within the granulosa-luteal layer, as well as helper and suppressor T cells within the thecal trabeculae, suggest a possible role for these immune cells in the ovary (Petrovska *et al*., 1992). Interestingly, granulosa-lutein cells exhibit increased staining for class II MHC antigens during the late luteal phase, concurrent with T cell invasion (Bukovsky *et al*., 1995).

Secretion of cytokines, chemokines and growth factors

Macrophages are major secretory cells capable of releasing cytokines, chemokines and growth factors that function in normal, inflammatory and disease processes of most tissues. A selection of macrophage products and their established functions is given in Figure 2. In general, the production and release of these secretory proteins is tightly regulated in temporal and tissue-specific manners by paracrine and autocrine regulatory mechanisms.

Cytokines are small proteins (15–60 kDa) that act locally through specific cell surface receptors to coordinate interactions of the immune system and surrounding tissues. Macrophages secrete a diverse repertoire of cytokines, including interleukin (IL)-1, -6, -10, and -12, interferon α (IFNα), tumour necrosis factor α (TNFα), and granulocyte macrophage-colony stimulating factor (GM-CSF). These cytokines have been identified in the ovary of many species and are known to impact many aspects of ovarian function (reviewed by Brannstrom and Norman, 1993; Terranova and Rice, 1997; Bukulmez and Arici, 2000) including follicle growth and differentiation, ovulation, and corpus luteum formation and function, as detailed in subsequent sections.

Macrophages also produce and secrete chemokines, small (60–70 amino acids) chemotactic cytokines containing conserved cysteine residues, which are important mediators of leukocyte recruitment and activation. Chemokines consist of two families: the C-C family, potent chemoattractants for monocytes/macrophages, includes monocyte chemoattractant protein (MCP)-1 and MCP-3, and RANTES (regulated upon activation, normal T cell expressed and secreted), and the C-X-C family, which selectively recruits neutrophils, includes IL-8, epithelial-derived neutrophil attractant-78 (ENA-78), and growth-regulated oncogene α (GROα). Several chemokines have been identified in the rat ovary (Wong *et al*., 2002), some of which are hormonally regulated.

Growth factors secreted from macrophages include epidermal growth factor (EGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF) α and β, each of which is important for normal ovarian function. These growth factors are also expressed by granulosa and theca cells, but macrophages have been largely neglected as

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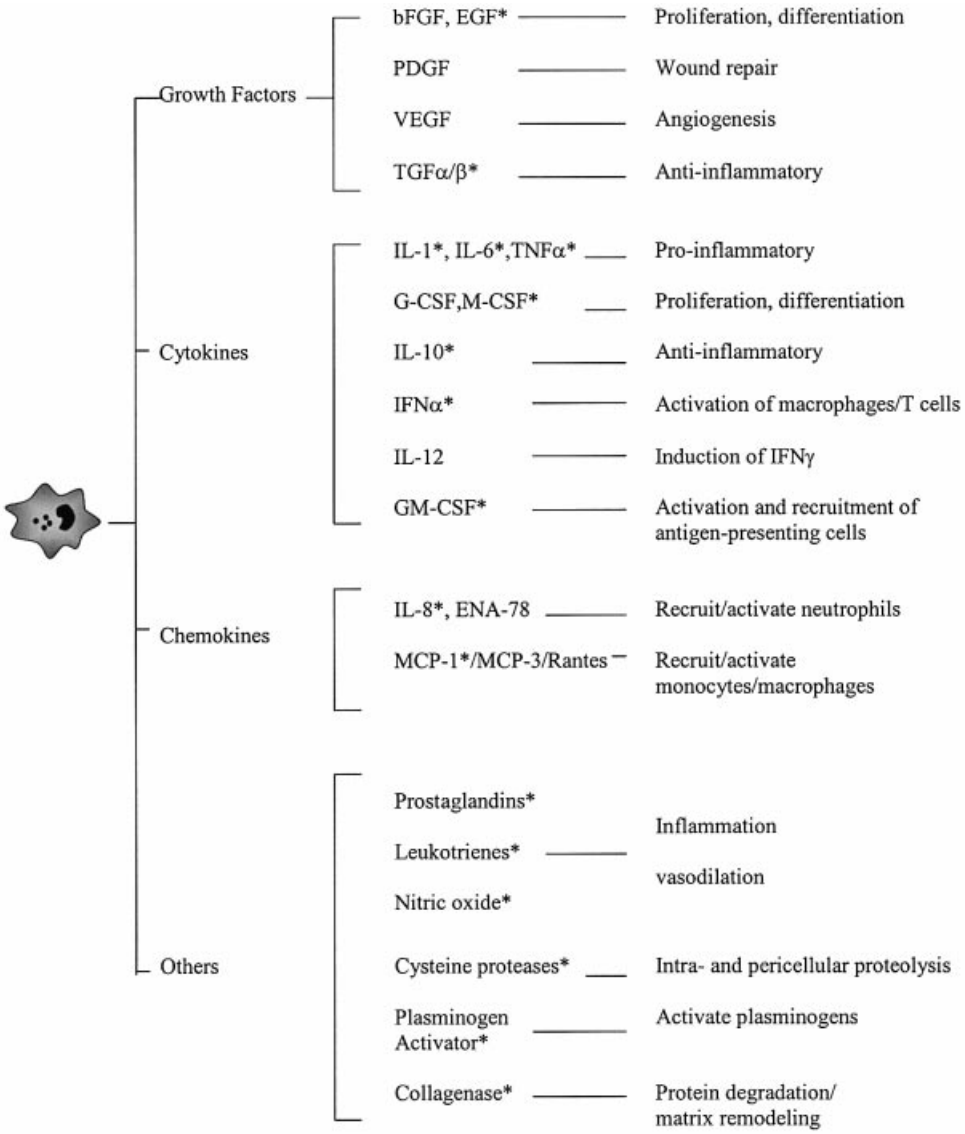

Figure 2. Macrophage products and functions. *Macrophage products which have been detected in the ovary. (Compiled from Nathan, 1987; Sprugel *et al*., 1987; Rappolee *et al*., 1988; Sunderkotter *et al*., 1994; Krakowski *et al*., 2002; Junttila *et al*., 2003.)

another potential source in the ovary. In the rat ovary, however, EGF was detected in macrophages surrounding developing follicles (Katabuchi *et al*., 1996) and TGFβ was detected in macrophages within functional corpora lutea (Matsuyama and Takahashi, 1995), indicating that during specific phases of the ovarian cycle macrophage-derived growth factors are likely to influence neighbouring cells in a paracrine manner. In the case of IGF-I, although it is produced by some macrophages (Nagaoka *et al*., 1990; Sunderkotter *et al*., 1994), it has not yet been localized to these cells in the ovary. However, since IGF has been found to modulate monocyte proliferation (Long *et al*., 1998) and macrophage cytokine production *in vitro* (Renier *et al*., 1996), IGF (as well as other growth factors) produced by granulosa and theca cells are likely to reciprocally regulate macrophage effector functions.

Definitive experiments identifying which cytokines and growth factors derived from macrophages are important for ovarian function are greatly lacking, due to the ubiquitous production of many of these factors by multiple ovarian cell types: granulosa cells, theca cells and macrophages. This knowledge gap, however, can be resolved by emerging techniques that specifically isolate ovarian macrophages, in order to better characterize their patterns of gene expression and protein production. For example, ongoing experiments from our own group have revealed that in isolated ovarian macrophages, the mRNA and protein expression of several cytokines is hormonally controlled (K.H.Van der Hoek, unpublished data), providing evidence that macrophage-derived factors are influencing follicular function at precise stages in the ovarian cycle.

Secretion of proteolytic enzymes

Macrophages have the capacity to produce and release a highly diverse group of proteolytic enzymes (Owen and Campbell, 1999a) which are able to degrade ECM, and activate or inhibit

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downstream protease cascades, as well as alter bioactive proteins such as leukocyte adhesion molecules, matrix-bound growth factors and membrane-bound cytokines (Owen and Campbell, 1999b; Bauvois, 2001). Highlighted here will be proteases that can be produced by macrophages and that have also been shown to be relevant in the ovary.

The cysteine proteases, cathepsins S, L, B, H and D are produced by and localized to the lysosomes of most cells, including macrophages and some macrophages also have the specialized ability to secrete these enzymes for pericellular matrix degradation (Owen and Campbell, 1999b). Each of these cathepsins has been detected in the mouse ovary and exhibits distinct patterns of cellular localization and hormonal regulation (Oksjoki *et al*., 2001). Although not definitively attributable to macrophages, some cathepsin proteins are preferentially expressed in macrophage-rich regions of the ovary such as the theca layer, corpus luteum and atretic follicles (Dhanasekaran and Moudgal, 1986; Oksjoki *et al*., 2001).

Serine proteases produced by macrophages include human leukocyte elastase, proteinase 3, and cathepsin G. Another member, urokinase-type plasminogen activator (uPA), cleaves plasminogen to proteolytically active plasmin and has been extensively studied in macrophages (Saksela *et al*., 1985; Dewerchin *et al*., 1996) as well as the ovary (reviewed by Ny *et al*., 2002). In the mouse ovary, in response to ovulatory gonadotrophin (LH/hCG), there is induced expression of uPA, as well as tissue-type plasminogen activator (tPA) in cells throughout the ovarian stroma which are reminiscent of ovarian macrophages, in addition to the high levels in granulosa cells (Hagglund *et al*., 1996).

Macrophages primarily produce matrix metalloproteinases (MMP), including: MMP-1 (collagenase); MMP-2 and MMP-9 (gelatinases); MMP-3, MMP-10 and MMP-11 (stromelysins); and MMP-7 (matrilysin) (Owen and Campbell, 1999a). Each of these MMP has also been detected in the ovary of several species (Hagglund *et al*., 1999; Ricke *et al*., 2002) and in general MMP are thought to regulate multiple aspects of ovarian function (reviewed by Curry and Osteen, 2001). Although studies have not specifically addressed production by ovarian macrophages, many MMP are expressed in the macrophage-rich regions of the ovary. MMP-2, MMP-9 and MMP-1 (MMP-13 in the rodent), for example, are expressed and active in the theca cell layers concurrent with ovulation (Hagglund *et al*., 1999; Curry and Osteen, 2001; Curry *et al*., 2001). Both MMP-14 [also known as membrane-type (MT)1-MMP] and MMP-19 are also rapidly expressed in response to ovulatory LH/hCG in scattered cells surrounding preovulatory follicles (a macrophage-like pattern) prior to expression in granulosa cells (Hagglund *et al*., 1999). MMP-3, MMP-7 and MMP-11 are up-regulated in ovarian regions undergoing apoptosis, concurrent with macrophage infiltration into these sites (Hagglund *et al*., 2001; Ricke *et al*., 2002). Also of interest, there are a number of MMP that are targeted for transmembrane expression on the cell surface, allowing for even greater control of protease localization within tissues (Bauvois, 2001). These proteases include members of the ADAM (a disintegrin and metalloprotease) family, such as TACE (TNFα convertase), and members of the MT-MMP family whose expression in the ovary is only beginning to be addressed.

Remodelling of ECM and release/activation of bound effector molecules occurs during many phases of ovarian function and requires precise regulation and appropriate localization of proteolytic enzymes. Thus, by virtue of their ability to be specifically recruited into particular ovarian regions, macrophages represent a possible mechanism by which to tightly control ovarian proteolysis.

Cumulatively, the above studies demonstrate that macrophages can be identified using multiple marker proteins and are present in the ovary of many species. Macrophages are able to: (i) phagocytose cellular debris and present antigens, (ii) secrete cytokines, chemokines and growth factors, and (iii) produce proteases that mediate matrix dissolution; thereby enabling them to influence multiple aspects of ovarian function (Figure 1). The following sections will focus on stages of ovarian follicle and corpus luteum development and describe the functional contributions of macrophages to each phase.

Roles of macrophages and macrophage-derived molecules in ovarian function

The ovary is composed of growing and atretic follicles, developing and regressing corpora lutea, and stromal/interstitial tissue. All components are present simultaneously in the adult ovary, with varying proportions of each dependent on the ovarian cycle stage. Interactions between the ovarian steroid hormones and the gonadotrophins from the pituitary are primary regulators of the ovarian cycle; however, many data suggest that macrophages, through their trophic functions in reproductive tissues, are essential accessory cells for optimal fertility (Norman and Brannstrom, 1994; Cohen *et al*., 1999).

The presence of macrophages in the ovary has been established for many years. Their identification was the result of studies carried out in 1964 examining the distribution of the macrophage enzymes alkaline phosphatase, esterase and β-glucuronidase in the rat ovary (Bulmer, 1964). Their specifically localized distribution and temporal variations during the cycle (Figure 3) suggest that macrophages play multiple roles in intraovarian events. Their ability to regulate ovarian cellular proliferation, inflammation and steroidogenesis further implicate these cells as regulators of ovarian function.

Regulation of follicular growth and atresia

Follicle growth occurs when small follicles are recruited to undergo granulosa and theca cell proliferation and antrum formation in response to FSH, estrogens and other locally produced factors. Only a fraction of growing follicles, however, reach the preovulatory stage and ultimately ovulate. The majority succumb to follicular atresia whereby granulosa cells undergo apoptosis and the follicle regresses and is resorbed by the ovary.

Direct interactions between macrophages and primordial follicles have not been observed, thus the earliest phases of follicle growth appear to be independent of macrophage influences. During follicle growth, however, the distribution of ovarian macrophages changes and they increase in number and localize to the theca cell layer of healthy follicles (see Figure 3B and C).

Two interesting rodent models exhibit reduced numbers of ovarian macrophages as well as reduced follicle growth and impaired fertility. The first, osteopetrotic (op/op) mice, have

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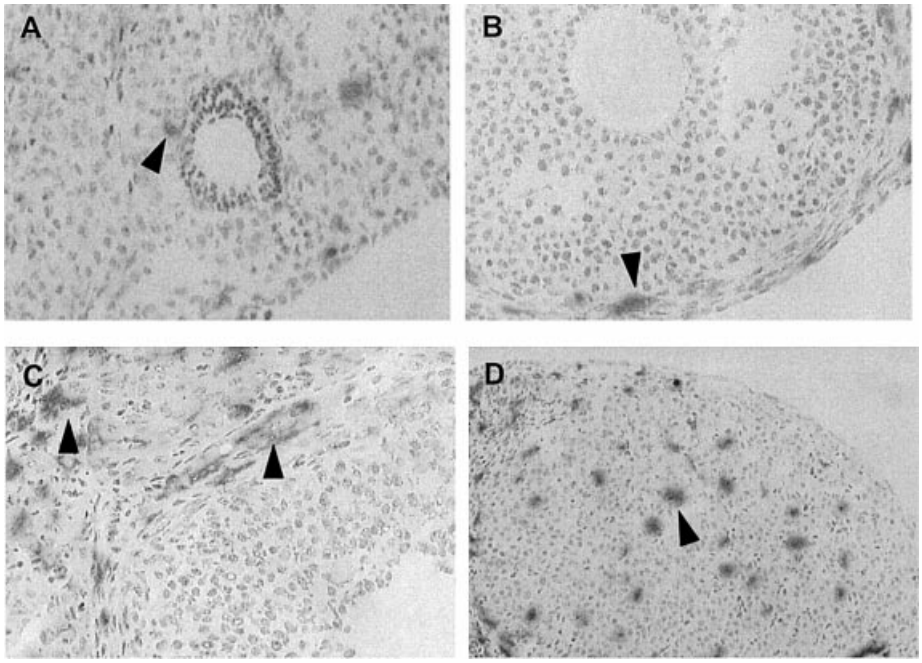

Figure 3. Immunohistochemical localization of MHC class II positive macrophages (arrowheads) in the murine ovary (provided by K.H.Van der Hoek). Macrophages are present in many areas of the ovary including stroma surrounding primary follicles (**A**), the thecal layers of preantral follicles (**B**), the interstitium and thecal layers of preovulatory follicles (**C**), and the corpus luteum (**D**). Magnifications: **A**, **B** and **C**, ×800; **D**, ×400.

severely reduced numbers of mature macrophages due to a natural mutation in the CSF-1 gene. These mice have a hypothalamic lesion that impacts estrus cyclicity (Cohen *et al*., 2002) but also exhibit reduced numbers of ovarian macrophages, which may be either a cause or effect of the decreased follicle growth. Secondly, feed restriction in rats also reduces the numbers of macrophages surrounding preovulatory follicles (Duggal *et al*., 2002), providing an interesting link between nutrition and ovarian macrophage populations.

The activation status of ovarian macrophages is also likely to be regulated during follicle growth. During early stages of rodent follicular development, CSF-1 both increases the number of ovarian macrophages and up-regulates macrophage scavenger receptor activity (Nishimura *et al*., 1995). Also concurrent with follicle growth, there is increased synthesis and release of the cytokine GM-CSF from ovarian macrophages, as well as theca-interstitial cells (Tamura *et al*., 1998).

It is thought that macrophages located in the theca of growing follicles, by secreting growth factors and/or cytokines, play a synergistic role in stimulating cellular proliferation and follicle growth, and in suppressing follicular apoptosis. Indeed, co-culture of rat granulosa cells with peritoneal macrophages results in proliferation of the granulosa cells (Fukumatsu *et al*., 1992). Some of the macrophage-derived factors that are known to impact follicular growth are hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), EGF, TGFα/β, and IGF. There are many studies that demonstrate the influences of these factors on ovarian cell types (reviewed by Geva and Jaffe, 2000; Monget and Bondy, 2000; Ingman and Robertson, 2002; Richards *et al*., 2002) with a subset of examples detailed below. Although macrophages are not the only source of these factors in the ovary, their localization to specific follicle types makes it likely that they exert paracrine influences. HGF can be produced by activated macrophages (Kodelja *et al*., 1997), receptors for this factor can be found in growing follicles (Yang and Park, 1995) and HGF stimulates granulosa cell proliferation and prevents granulosa cell apoptosis *in vitro* (Parrott *et al*., 1994). bFGF is a major regulator of angiogenesis that is also produced by macrophages (Sunderkotter *et al*., 1994). bFGF plays a role in the regulation of granulosa cell mitosis and differentiation, thecal cell differentiation and can prevent the spontaneous apoptosis of granulosa cells that occurs in culture (Oury *et al*., 1992; Tilly *et al*., 1992). EGF and TGFα have been demonstrated to be present in cells of the thecal layer in the rat (Kudlow *et al*., 1987; Skinner *et al*., 1987), bovine (Skinner and Coffey, 1988) and human (Scurry *et al*., 1994) ovary. EGF stimulates follicle DNA synthesis to a degree equivalent to that of FSH in the hamster (Roy and Greenwald, 1991), and in gonadotrophin-primed immature rats can stimulate granulosa cell proliferation and modulate follicular development through a paracrine mechanism (Fukumatsu *et al*., 1995; Katabuchi *et al*., 1996). TGFβ is also well known to potentiate the effects of FSH on granulosa cell DNA synthesis and follicle growth (Ingman and Robertson, 2002). Similarly, IGF amplify gonadotrophin-stimulated proliferation and steroidogenesis in ovarian cell types (Monget *et al*., 1996).

Macrophages are only found in the granulosa cell layer at advanced stages of atresia (Petrovska *et al*., 1996) and because they are known to phagocytose apoptotic cells it is thought that they participate in the removal of cell debris created during granulosa cell apoptosis (Takaya *et al*., 1997; Gaytan *et al*., 1998a). However, they may also have an active role in the production of factors promoting follicular atresia. Cytokines produced by macrophages *in vitro*, particularly TNFα (Kaipia *et al*., 1996), induce apoptosis in ovarian cell types and follicles,

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which supports this theory. In contrast, *in vitro* experiments show that both EGF and TGFα can prevent spontaneous apoptosis of follicles or isolated granulosa cells (Tilly *et al*., 1992). Thus whether macrophages are strictly involved in removal of apoptotic cells or whether they are involved in the initiation of apoptosis and atresia is not clear and must be addressed in future studies.

In short, macrophages and/or macrophage-derived products are important mediators of follicle development via regulating the balance between cellular proliferation and apoptosis, as well as angiogenesis and steroidogenesis. Thereby, they have the ability to influence processes that either commit or rescue follicles from atresia.

Presence in human follicular fluid

A study examining periovulatory human follicular fluid from IVF cycles found considerable numbers of macrophages and monocytes in this fluid, and documented their presence in normal human ovary tissue sections (Loukides *et al*., 1990). Although granulosa-luteal cells predominate in follicular fluid aspirates, it was found that 5–15% of the cells are macrophages and monocytes. Baranao *et al*. (1995) evaluated macrophage and HLA positive cells in the follicular fluid and found that human follicular fluid contained ~10% macrophages but that only 7.85% were ovarian-derived and the rest attributed to contamination with peripheral blood monocytes.

Because macrophages are a significant component of the intrafollicular compartment, many studies have been undertaken to evaluate whether macrophage-derived cytokines are also present in human follicular fluid. Levels of IL-1β, IL-6, IL-10 and GM-CSF in follicular fluids have been measured in multiple studies (Wang and Norman, 1992; Calogero *et al*., 1998). IVF patients with infertility due to immunological causes had higher levels of TNFα and IL-6 and lower concentrations of GM-CSF in their periovulatory follicular fluid compared to patients with tubal factor infertility (Cianci *et al*., 1996; Calogero *et al*., 1998). Follicular fluid-derived cells express IL-1β mRNA which may be a product of macrophages, granulosa cells, or both (Loukides *et al*., 1990; Baranao *et al*., 1995). Moreover, co-culture of follicular fluid-derived macrophages and granulosa cells from ovulatory follicles resulted in increased numbers of IL-1β-producing granulosa cells (Machelon *et al*., 1995).

Macrophages are a prevalent cell type in human follicular fluid aspirates and represent an important source of follicular fluid cytokines that are likely to be involved in follicle growth and ovulation. Much work is necessary, however, to determine how alterations in macrophage numbers, activation status or cytokine production correlate with follicular dysfunction in infertile women from whom the follicular fluid is obtained.

Roles in ovulation

Ovulation involves the rupture of preovulatory follicles at the surface of the ovary and extrusion of the oocyte into the oviduct. The hypothesis that mammalian ovulation is comparable to an inflammatory reaction, sharing the characteristics of edema, vasodilation, heat and pain, was first proposed by Espey (1980). In gonadotrophin-primed immature rats, there is an increase in ovarian blood volume, edema due to vasodilation and increased vascular permeability within a few hours of hCG treatment, which persists to the time of follicular rupture (Tanaka *et al*., 1989).

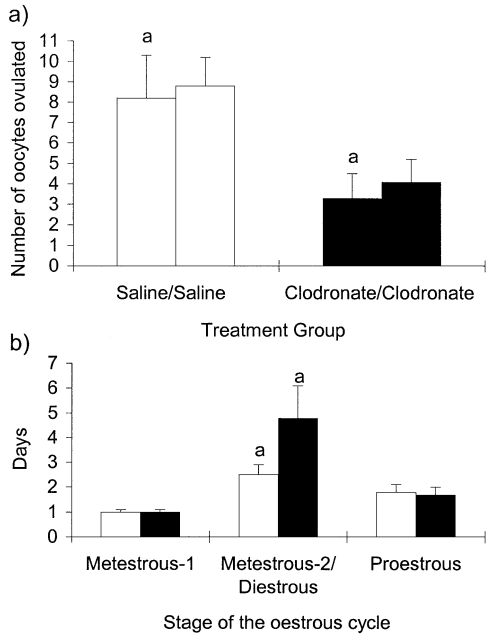

Figure 4. The effect of ovarian macrophage depletion in the mouse by intrabursal injection of clodronate liposomes. Macrophage depletion of each ovary with clodronate (black bars) resulted in a reduction in ovulation rate (**a**) and extension of the estrous cycle (**b**), particularly in the metestrous-2/ diestrous stage, compared to saline treated ovaries (white bars). Bars with the same letter are significantly different from each other ($P < 0.05$). (Adapted from Van der Hoek et al., 2000.)

Inflammatory mediators such as prostaglandins, leukotrienes, bradykinin, histamine, PAF and multiple cytokines have been found to be associated with the ovulatory process. The increased vascular permeability and edema are temporally associated with dissolution of thecal collagen and ECM, which culminates in follicular rupture (Bjersing and Cajander, 1974; Abisogun *et al*., 1988).

Immediately prior to ovulation, there is increased macrophage migration into the thecal layers of preovulatory follicles (see Figure 3C) as described in the rat (Brannstrom *et al*., 1993a) and human (Brannstrom *et al*., 1994b). This periovulatory increase in macrophage recruitment is likely to be a response to local modulation of chemokine production; for instance, LH/hCG induces MCP-1 mRNA in the rat ovary (Wong *et al*., 2002) and in cultured human granulosa lutein cells (Arici *et al*., 1997).

This pronounced increase in macrophage number occurs specifically in the theca of healthy preovulatory follicles (Brannstrom *et al*., 1994b) and macrophages have been shown to be essential potentiators of the ovulation process (Van der Hoek *et al*., 2000; Brannstrom and Enskog, 2002). Supplementing the media of a perfused preovulatory rat ovary with blood leukocytes increases the numbers of oocytes released following the administration of LH (Hellberg *et al*., 1991), suggesting that immune cells have a role in the complex ovulatory cascade. More specifically, in the mouse, we have shown that depletion of ovarian macrophages by intrabursal clodronate liposome treatment decreases ovulation rate, as well as delays progression through the subsequent estrous cycle (Figure 4) (Van der Hoek *et al*., 2000).

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Macrophages have the capacity to release numerous cytokines demonstrated to be important in the ovulatory process, particularly IL-1β (Adashi, 1998) and TNFα (Brannstrom *et al*., 1995). IL-1β levels increase in the ovary as ovulation approaches (Brannstrom *et al*., 1994a), addition of IL-1β to the media of *in vitro*-perfused ovaries stimulates ovulation in the rat (Brannstrom *et al*., 1993c) and rabbit (Takehara *et al*., 1994), and injection of the IL-1 receptor antagonist (IL-1RA) inhibits ovulation *in vivo* (Peterson *et al*., 1993; Simon *et al*., 1994b). Furthermore, nitric oxide (NO), an important mediator of the pro-inflammatory actions of IL-1β, is essential for optimal ovulation rate as demonstrated by mutant mouse models (reviewed by Dixit and Parvizi, 2001), and suppression of NO production with the pharmacological inhibitor L-NAME reduces both the number of ovarian leukocytes and the IL-1β-stimulated ovulation rate (Bonello *et al*., 1996). Expression of TNFα mRNA and protein has been localized to macrophage-like cells within the ovarian interstitium (as well as other ovarian cell types) (Chen *et al*., 1993) and this cytokine has also been shown to stimulate LH-induced ovulation in the perfused rat ovary (Brannstrom *et al*., 1995) as well as induce production of ovulatory mediators in pre-ovulatory rat follicles cultured *in vitro* (Brannstrom *et al*., 1993b). It has also been proposed that the release of TNFα by cells within the thecal layer stimulates local cellular apoptosis, thus facilitating follicular rupture (Murdoch *et al*., 1997).

The production of proteinases at the apex of the preovulatory follicle is essential for degradation of the basement membrane and the follicular wall at ovulation. Inhibition of collagenase/proteinase activity results in the inhibition of ovulation (Brannstrom *et al*., 1988; Butler *et al*., 1991); however, the identity of the critical ovulatory protease(s) has not yet been elucidated. As described above, macrophages and monocytes produce a diverse array of proteinases cumulatively capable of degrading all types of matrix proteins (Werb *et al*., 1980; Owen and Campbell, 1999a). It has therefore been proposed that macrophages in the theca of the preovulatory follicle produce proteolytic factors under the influence of locally produced paracrine or autocrine regulators. For instance, macrophages are known to produce plasminogen activator which, when perfused into the rabbit ovary, rapidly triggers ovulation (Yoshimura *et al*., 1987). Also, mice which are doubly deficient in the plasminogen activators tPA and uPA exhibit impaired ovulation (Leonardsson *et al*., 1995). The protease proprotein convertase 4 (PC4) has been localized to macrophage-like cells in the mouse ovary and shown to regulate cytokine production by these cells (Tadros *et al*., 2001). Interestingly, mice null for PC4 protease exhibit decreased ovarian weight, decreased progesterone production and decreased litter size (Mbikay *et al*., 1997), providing a compelling link between ovarian macrophage proteases and female fertility.

Macrophages have been shown to be important potentiators of ovulation, but the essential secondary messengers remain to be conclusively identified. To date, proteases and cytokines are the most likely candidates for the macrophage-derived products that facilitate ovulation.

Regulation of corpus luteum formation and regression

After ovulation, a complete reorganization of the ruptured follicle is required to produce a corpus luteum. This is characterized by terminal differentiation (luteinization) of granulosa cells, migration of leukocytes, including macrophages, into the luteinizing follicle and neo-vascularization of the developing corpus luteum. Class II MHC positive macrophages are the most prominent immune cells within the human corpus luteum throughout its lifespan (Petrovska *et al*., 1992; see also Figure 3D). Several studies have analysed macrophages during corpus luteum lifespan, but the utilization of different macrophage markers has complicated interpretation of the results. Macrophages have been described predominantly in the theca-lutein layer (Lei *et al*., 1991; Wang *et al*., 1992) at a maximum in the late luteal phase (Duncan *et al*., 1998). Another study found that in the human ovary the number of CD68 positive macrophages increased up to the end of the early luteal phase, remained relatively unchanged during the midluteal phase, and decreased at the late luteal phase (Gaytan *et al*., 1998b), paralleling the functional activity of the corpus luteum. Another study, however, found that the proportion of macrophages in the human corpora lutea did not differ between different stages of the luteal phase (Castro *et al*., 1998).

The activation status of macrophages is likely to be important for their effector functions within the corpus luteum. Macrophages showed round or elongated cytoplasm during the early and late luteal phases and displayed dendritic features in the mid-luteal phase, morphological changes typically related to their activation state (Gaytan *et al*., 1998b). Takaya *et al*. (1997) also reported both round and spindle-shaped macrophages within the corpus luteum depending on the luteal stage (Takaya *et al*., 1997). GM-CSF regulates many aspects of macrophage differentiation and activation (Inaba *et al*., 1992) and ovarian macrophages from mice lacking GM-CSF exhibit decreased expression of activation markers, including class II MHC and CD11b/Mac-1 (Jasper *et al*., 2000). These mice also have decreased ovarian weight and decreased progesterone production at day 4 of pregnancy, indicating that GM-CSF has a role in modulating the activation status of ovarian macrophages, which has consequences for appropriate progesterone production (Jasper *et al*., 2000).

Macrophages may facilitate the establishment of the vasculature in the corpus luteum via secretion of VEGF, EGF and bFGF, which would influence aspects of angiogenesis (Sunderkotter *et al*., 1994). VEGF, for instance, stimulates proliferation *in vitro* of microvascular endothelial cells obtained from the primate corpus luteum (Christenson and Stouffer, 1996). Macrophages may also increase progesterone production in the forming corpus luteum. The culture of peritoneal macrophages with luteinizing granulosa cells resulted in increased levels of progesterone production (Chen *et al*., 1992), and several macrophage-derived factors such as IL-1β, EGF and TNFα (Serta and Seibel, 1993; Yan *et al*., 1993; Chen *et al*., 2000) have also been shown to stimulate progesterone production. In contrast, there are also reports that progesterone secretion is markedly inhibited in co-cultures of granulosa cells with peritoneal macrophages. Here the degree of inhibition was dependent on both the number and activation status of the co-cultured macrophages (Shakil and Whitehead, 1994).

The number of macrophages in the corpus luteum is highest during regression, implicating these cells in luteolysis (Paavola and Boyd, 1979; Lei *et al*., 1991; Brannstrom *et al*., 1994b; Hameed *et al*., 1995; Best *et al*., 1996; Senturk *et al*., 1999). Inflammatory cell infiltration begins in the theca lutein and gradually invades the granulosa lutein, but this infiltration can be prevented by inhibition of luteolysis with hCG to mimic

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pregnancy (Duncan *et al*., 1998). In the human, the progressive infiltration of lymphocytes and macrophages during luteal regression may occur in response to MCP-1 expression in blood vessels within the corpus luteum (Hameed *et al*., 1995). In the rat, increased endothelial cell expression of the intercellular adhesion molecule (ICAM)-1 occurs concurrently with macrophage infiltration, suggesting that ICAM-1 mediates macrophage migration into the regressing corpus luteum (Olson *et al*., 2001). The influx of macrophages also coincides with increased MMP activity in luteal cells (Duncan, 2000) and increased macrophage phagocytosis (Takaya *et al*., 1997), both of which are thought to be important for ingestion of cellular remnants that result from luteal cell apoptosis (Pate and Landis Keyes, 2001).

The process of luteolysis and regression is known to involve increased synthesis of prostaglandin F_{2a} (PGF_{2a}), decreased progesterone production and luteal cell apoptosis, and macrophages may impact each of these stages. Macrophages may be one source of PGF_{2a} or, via TNFα secretion, may stimulate PGF_{2a} production by luteal cells (Benyo and Pate, 1992; Wang *et al*., 1992). Macrophages may also inhibit progesterone production directly, since removal of leukocytes from luteal cell cultures has been shown to increase progesterone levels (Kohen *et al*., 1999). TNFα has also been shown to inhibit progesterone secretion by mouse luteal cells (Adashi *et al*., 1990) and TNFα and IL-1β both decrease progesterone production and inhibit survival of bovine luteal cells (Benyo and Pate, 1992). Macrophages also have the capacity to secrete factors that may stimulate apoptosis in the corpus luteum, such as reactive oxygen intermediates, and particularly TNFα. TNFα mRNA has been observed in the corpus luteum of the mouse (Chen *et al*., 1993), human (Kondo *et al*., 1995) and rat (Marcinkiewicz *et al*., 1994), and in the rabbit, where it was associated with macrophage numbers (Bagavandoss *et al*., 1988; Bagavandoss *et al*., 1990). In the bovine corpus luteum, TNFα induces apoptosis, via the TNFα receptor type I, specifically in endothelial but not steroidogenic cells (Friedman *et al*., 2000). In the porcine corpus luteum, macrophages appear to be the primary source of TNFα (Zhao *et al*., 1998).

In summary, there are multiple aspects of luteal function that are influenced by ovarian macrophages and/or their secreted products: progesterone secretion, vascularization, prostaglandin production, and apoptosis. In addition, there is evidence that T cell-mediated responses are involved in luteal regression (Pate and Landis Keyes, 2001; Komatsu *et al*., 2003). Thus macrophage activation of T cells may be an additional, indirect means of influencing luteal regression that needs to be investigated in greater detail.

Macrophages in ovarian dysfunction and disease

Many diseases have an immune component, demonstrating that leukocytes exert important effects on tissues which, when misregulated, can lead to dysfunction and pathology. Macrophage effector functions are precisely regulated by temporal and tissue-specific mechanisms. Furthermore, macrophage-mediated effects on ovarian function are complex: they impact multiple aspects of ovarian function and are precisely regulated by hormone, cytokine and matrix signals. There is emerging evidence that macrophages and macrophage-derived products are involved in some ovarian dysfunctions, particularly polycystic ovary syndrome (PCOS), endometriosis and premature ovarian failure (POF).

Polycystic ovary syndrome

PCOS is the most common hormonal disorder of young women, estimated to affect 5–10% of women through and beyond their reproductive years. The prevalence of affected individuals and the wide range of related phenotypes are thought to be due to both genetic and environmental factors (Crosignani and Nicolosi, 2001). PCOS results in anovulation and therefore impaired fertility, but is a multisystem disorder which is also associated with hyperinsulinaemia, hyperlipidaemia, diabetes mellitus, obesity, hyperandrogenemia, hirsuitism, acne and increased incidence of endometrial cancer (Norman and McVeigh, 1999; Norman, 2001). It has also been reported that PCOS patients exhibit chronic low-grade inflammation, manifested as elevated levels of C-reactive protein (Kelly *et al*., 2001). The fact that immune-modulating treatments, such as dexamethasone, are often used to alleviate PCOS symptoms provides further evidence of the involvement of leukocytes in this syndrome. Another treatment option for PCOS is laparoscopic laser drilling which involves piercing the ovarian surface. This method is thought to work by inducing a pro-inflammatory response in the ovary which would facilitate ovulation; indeed studies in the sheep have shown that laser drilling results in the influx of macrophages and lymphocytes (Tozawa *et al*., 1995). More recently, however, the literature has focused on experiments and clinical trials involving the treatment of PCOS-associated obesity and insulin-resistance. Interestingly, the most effective agents used in the treatment of PCOS are anti-diabetic drugs metformin and troglitazone (an agonist of the PPARγ receptor). PPARγ ligands are well studied for their insulin-sensitising abilities in adipocytes; however, they also exert potent anti-inflammatory effects in macrophages (Tontonoz and Nagy, 1999; Lee and Evans, 2002). In PCOS patients these pathways may be causally linked as metformin treatment not only improves insulin sensitivity in PCOS patients but also reduces inflammation, measured as C-reactive protein levels (Morin-Papunen *et al*., 2003). Future studies are therefore likely to show an important link between macrophage activation status, obesity/insulin resistance and severity of PCOS symptoms.

Proper follicle development is dependent on the appropriate cytokine and growth factor milieu, as detailed above, and macrophages represent an important source of these factors. Numerous studies have therefore compared serum and follicular fluid cytokine levels in PCOS patients to non-PCOS patients, with conflicting results such that no clear picture has emerged. In a group of PCOS patients that had received no ovarian stimulation, TNFα in follicular fluid was reported to be no different than normal levels (nor were IL-1β levels different) (Jasper and Norman, 1995). Yet, in a study of non-obese/non-diabetic PCOS patients treated with gonadotrophins, serum and follicular fluid TNFα and IL-6 levels were elevated compared to normal controls (Amato *et al*., 2003). In a group of obese PCOS patients, dexamethasone treatment was seen to alter follicular fluid cytokine levels indicating that immune cells are likely to be at least partially involved in the production of follicular fluid cytokines. In this study IL-6 levels were unchanged but CSF-1 levels were increased, and TNFα levels were reduced and associated with increased follicular estradiol compared to untreated PCOS patients (Zolti *et al*., 1992). Cumulatively these reports suggest that in at least some instances women with PCOS exhibit elevated follicular

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and/or serum cytokine levels which are likely to be involved in the observed alterations in follicular maturation and ovarian function.

Studies in sheep and rhesus monkey models have shown that when pregnant animals are administered testosterone, the female offspring exhibit PCOS-like ovaries with characteristic cysts. In these models it is thought that elevated prenatal androgens developmentally program LH hypersecretion and ovarian steroid production, which can further augment androgen action (Abbott *et al*., 2002). Studies in mice have also shown that neonatal exposure to estradiol results in cystic ovaries that produce elevated levels of TNFα and IL-6, similar to many cases of PCOS. Interestingly, peritoneal macrophages from these mice also produce elevated levels of TNFα and IL-6, indicating that cytokine production by macrophages is altered systemically (Deshpande *et al*., 2000). Although these animal models have made some inroads into our understanding of immune involvement in PCOS, more work is clearly necessary. In particular, genetically targeted mouse models that exhibit PCOS-like ovaries are lacking and represent an important goal for future research that would begin to shed light on the molecular mechanisms of this complicated disease.

Endometriosis

Endometriosis, a condition that is characterized by the presence and growth of endometrial cells outside the uterus, is estimated to affect 3–10% of women of reproductive age and 25–35% of infertile women (Olive and Schwartz, 1993). Endometriosis is frequently found in the ovaries as well as the anterior and posterior cul-de-sac, the uterosacral ligaments and broad ligament of the uterus, and is often associated with pelvic pain and infertility. Although the pathogenesis of endometriosis and the mechanism of endometriosis-associated infertility remains unclear, endometriosis has been implicated as a factor in disordered and/or retarded follicle growth and ovulatory dysfunction as confirmed by ultrasonograghy, as well as in luteal phase defects (Doody *et al*., 1988).

Recent evidence suggests that leukocytes, including ovarian macrophages and their numerous products, may be involved in the onset and development of this disease (Vinatier *et al*., 1996). Macrophages infiltrating endometriotic stromal cells exhibit intense immunostaining and are a major source of soluble factors, particularly TGFβ, and may therefore be important regulators of cell proliferation in endometriotic cysts through their paracrine and autocrine actions (Tamura *et al*., 1999). Flow cytometric evaluation of leukocyte subpopulations present in follicular fluid of infertile women undergoing IVF has shown that the number of CD14 positive cells (macrophages/monocytes) is significantly increased in patients with endometriosis compared to those with tubal factor or idiopathic infertility, and it is suggested that they may adversely affect folliculogenesis or oocyte maturation (Lachapelle *et al*., 1996). It is suggested that $CD14^+$ cells may affect folliculogenesis or oocyte maturation and that their dysregulation in the ovary could be one of the factors impacting fertility.

Positive immunostaining for IL-6, a macrophage-derived cytokine, has been shown in the theca of antral follicles and in corpora lutea, areas coincident with the main locations of macrophages (Loret de Mola *et al*., 1996). Endometriotic stromal cells from 'chocolate cyst linings' of the ovary produced increased amounts of IL-6 compared with normal endometrial stromal cells (Tsudo *et al*., 2000). Other studies have shown that the follicular fluid of patients with endometriosis contains increased IL-6, which may be related to the inhibition of follicular development (Pellicer *et al*., 1998; Garrido *et al*., 2000; Pellicer *et al*., 2000). These data suggest that altered gene expression and protein secretion of IL-6, possibly by infiltrating macrophages in the ovarian endometriotic tissue, may contribute to the pathogenesis of this disease and/or to endometriosis-associated infertility (Tsudo *et al*., 2000). Bergqvist *et al*. (2001) showed that ovarian endometriotic tissue produces significantly higher concentrations of IL-6 and IL-1β than endometrium from healthy controls (Bergqvist *et al*., 2001). Another study, however, reported that IL-1β levels in follicular fluid were no different in these patients compared to normal controls, but confirmed increased levels of IL-6 (Pellicer *et al*., 1998).

VEGF and IL-8 concentrations were also found to be higher in the fluids of the ovarian endometriomas than in those of the follicular cysts of controls, indicating that angiogenesis could play an important role in the progression and maintenance of the ovarian endometriomas (Fasciani *et al*., 2000). VEGF concentrations in the follicular fluid from patients with endometriosis were lower than in the controls, but elevated VEGF levels have been correlated in IVF with good follicular vascularization and the health of the follicle (Van Blerkom *et al*., 1997).

The expression of IGF-I and its receptor has been detected in the stroma and epithelium in human ovarian endometriotic tissues. The expression of mRNA and immunohistochemical staining for TGFβ1 has also been detected in the epithelial lining and cellular stroma of ovarian endometriomas, which indicates that TGFβ1, IGF-I and their receptors might play an important role in the pathogenesis of endometriosis (Loverro *et al*., 2001). Tamura *et al*. (1999) confirmed the expression of TGFβ isoforms and receptors in endometriotic cysts, especially in the epithelial cells, in the human ovary (Tamura *et al*., 1999). A study of the localization of matrix metalloproteinases in ovarian endometriomas has shown that MMP-3 is mainly expressed in macrophages, which suggests that the destruction of the surrounding matrix by endometriosis might be caused by macrophage-derived MMP (Mizumoto *et al*., 2002).

The data reviewed here indicate that endometriosis is associated with altered levels of several specific cytokines and chemokines, many of which are known products and/or activators of macrophages. This, along with increased infiltration of leukocytes, is likely to contribute significantly to the pathology observed in this disease.

Premature ovarian failure

POF is defined as a syndrome characterized by cessation of ovarian function and menopause before the age of 40 years and is estimated to affect ~1% of the female population (Coulam *et al*., 1986). POF patients suffer from hypoestrogenism, anovulation and, in some cases, a variety of cellular immunity defects (Mignot *et al*., 1989). In particular, several autoimmune aetiologies have been identified. Using HLA class I molecules as markers for macrophages, some patients with autoantibodies were identified as having evidence of a defect in self-antigen presentation similar to that of type I diabetics (Hoek *et al*., 1997). In addition, there were significantly increased numbers of CD8 positive T cells in

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autoimmune POF patients. Hill *et al*. (1990) found that while in normal human ovaries only occasional cells of macrophage morphology were class II MHC positive and granulosa cells were negative, class II MHC antigen expression was prevalent on granulosa cells from POF patients, suggesting that POF might be associated with inappropriate expression of class II MHC antigen expression by granulosa cells, a phenomenon that can be mimicked by the *in vitro* culture of granulosa cells with the cytokine IFNγ (Hill *et al*., 1990). The cumulative data demonstrating autoimmune aetiologies and abnormal expression of leukocyte cell surface markers may assist in the development of tests which could result in early diagnosis, prior to complete ovarian failure (Yan *et al*., 2000).

The precise function of macrophages and their secretory products in ovarian disorders is still unclear, and more research is required to characterize the specific functions of ovarian macrophages, define their roles *in vivo* and determine how they may be dysregulated in disease.

Summary

Ovarian macrophages are important regulators of the complex communication between the immune and reproductive systems. They exhibit changes in numbers and phenotype depending on the stage of the estrus cycle, and, via secretion of a number of bioactive molecules, impact many ovarian processes. Macrophages are able to regulate cellular proliferation, differentiation and apoptosis, as well as influence steroid production, vascularization and tissue remodelling during follicle growth, ovulation and luteinization. It is hypothesized that alterations in the macrophage-mediated regulation of some of these processes contribute to the pathogenesis of ovarian disorders. Importantly, further studies on ovarian macrophages and their secretory products are needed in order to generate diagnostics, and eventually therapeutics, for ovarian diseases such as PCOS, endometriosis and POF.

References

Abbott DH, Dumesic DA and Franks S (2002) Developmental origin of polycystic ovary syndrome—a hypothesis. J Endocrinol 174,1–5.

Abisogun AO, Daphna-Iken D, Reich R, Kranzfelder D and Tsafriri A (1988) Modulatory role of eicosanoids in vascular changes during the preovulatory period in the rat. Biol Reprod 38,756–762.

Adashi EY (1998) The potential role of interleukin-1 in the ovulatory process: an evolving hypothesis. Mol Cell Endocrinol 140,77–81.

Adashi EY, Resnick CE, Packman JN, Hurwitz A and Payne DW (1990) Cytokine-mediated regulation of ovarian function: tumor necrosis factor alpha inhibits gonadotropin-supported progesterone accumulation by differentiating and luteinized murine granulosa cells. Am J Obstet Gynecol 162,889–896; discussion 896–899.

Aderem A and Underhill DM (1999) Mechanisms of phagocytosis in macrophages. Annu Rev Immunol 17,593–623.

Allen LA and Aderem A (1996) Mechanisms of phagocytosis Curr Opin Immunol 8,36–40.

Amato G, Conte M, Mazziotti G, Lalli E, Vitolo G, Tucker AT, Bellastella A, Carella C and Izzo A (2003) Serum and follicular fluid cytokines in polycystic ovary syndrome during stimulated cycles. Obstet Gynecol 101,1177–1182.

Arici A, Oral E, Bukulmez O, Buradagunta S, Bahtiyar O and Jones EE (1997) Monocyte chemotactic protein-1 expression in human preovulatory follicles and ovarian cells. J Reprod Immunol 32,201–219.

Austyn JM and Gordon S (1981) F4/80, a monoclonal antibody directed specifically against the mouse macrophage. Eur J Immunol 11,805–815.

Bagavandoss P, Kunkel SL, Wiggins RC and Keyes PL (1988) Tumor necrosis factor-a (TNF-a) production and localization of macrophages and T lymphocytes in the rabbit corpus luteum. Endocrinology 122,1185–1187.

Bagavandoss P, Wiggins RC, Kunkel SL, Remick DG and Keyes PL (1990) Tumor necrosis factor production and accumulation of inflammatory cells in the corpus luteum of pseudopregnancy and pregnancy in rabbits. Biol Reprod 42,367–376.

Baranao RI, Dain L, Palak de Fried E and Rumi LS (1995) Human granulosa cells express HLA-DR antigen and are capable of synthesizing interleukin-1. Horm Metab Res 27,495–498.

Bauvois B (2001) Transmembrane proteases in focus: diversity and redundancy? J Leukoc Biol 70,11–17.

Benyo DF and Pate JL (1992) Tumor necrosis factor-alpha alters bovine luteal cell synthetic capacity and viability. Endocrinology 130,854–860.

Bergqvist A, Bruse C, Carlberg M and Carlstrom K (2001) Interleukin 1beta, interleukin-6, and tumor necrosis factor-alpha in endometriotic tissue and in endometrium. Fertil Steril 75,489–495.

Best CL, Pudney J, Welch WR, Burger N and Hill JA (1996) Localization and characterization of white blood cell populations within the human ovary throughout the menstrual cycle and menopause. Hum Reprod 11,790–797.

Bjersing L and Cajander S (1974) Ovulation and the mechanism of follicle rupture VI Ultrastructure of theca interna and the inner vascular network surrounding rabbit graafian follicles prior to induced ovulation. Cell Tissue Res 153,31–44.

Bonello N, McKie K, Jasper M, Andrew L, Ross N, Braybon E, Brannstrom M and Norman RJ (1996) Inhibition of nitric oxide: effects on interleukin-1 beta-enhanced ovulation rate, steroid hormones, and ovarian leukocyte distribution at ovulation in the rat. Biol Reprod 54,436–445.

Bowen JM and Keyes PL (2000) Repeated exposure to prolactin is required to induce luteal regression in the hypophysectomized rat. Biol Reprod 63,1179–1184.

Brannstrom M and Enskog A (2002) Leukocyte networks and ovulation. J Reprod Immunol 57,47–60.

Brannstrom M and Norman RJ (1993) Involvement of leukocytes and cytokines in the ovulatory process and corpus luteum function. Hum Reprod 8,1762–1775.

Brannstrom M, Woessner JF Jr, Koos RD, Sear CH and LeMaire WJ (1988) Inhibitors of mammalian tissue collagenase and metalloproteinases suppress ovulation in the perfused rat ovary. Endocrinology 122,1715–1721.

Brannstrom M, Mayrhofer G and Robertson SA (1993a) Localization of leukocyte subsets in the rat ovary during the periovulatory period. Biol Reprod 48,277–286.

Brannstrom M, Wang L and Norman RJ (1993b) Effects of cytokines on prostaglandin production and steroidogenesis of incubated preovulatory follicles of the rat. Biol Reprod 48,165–171.

Brannstrom M, Wang L and Norman RJ (1993c) Ovulatory effect of interleukin-1 beta on the perfused rat ovary. Endocrinology 132,399–404.

Brannstrom M, Norman RJ, Seamark RF and Robertson SA (1994a) Rat ovary produces cytokines during ovulation. Biol Reprod 50,88–94.

Brannstrom M, Pascoe V, Norman RJ and McClure N (1994b) Localization of leukocyte subsets in the follicle wall and in the corpus luteum throughout the human menstrual cycle. Fertil Steril 61,488–495.

Brannstrom M, Bonello N, Wang LJ and Norman RJ (1995) Effects of tumour necrosis factor alpha (TNF alpha) on ovulation in the rat ovary. Reprod Fertil Dev 7,67–73.

Bukovsky A, Caudle MR, Keenan JA, Wimalasena J, Upadhyaya NB and Van Meter SE (1995) Is corpus luteum regression an immune-mediated event? Localization of immune system components and luteinizing hormone receptor in human corpora lutea. Biol Reprod 53,1373–1384.

Bukulmez O and Arici A (2000) Leukocytes in ovarian function Hum Reprod Update 6,1–15.

Bulmer D (1964) The histochemistry of ovarian macrophages in the rat. J Anat 98,313–319.

Butcher EC (1992) Leukocyte–endothelial cell adhesion as an active, multi-step process: a combinatorial mechanism for specificity and diversity in leukocyte targeting. Adv Exp Med Biol 323,181–194.

Butler TA, Zhu C, Mueller RA, Fuller GC, Lemaire WJ and Woessner JF Jr (1991) Inhibition of ovulation in the perfused rat ovary by the synthetic collagenase inhibitor SC 44463. Biol Reprod 44,1183–1188.

Calogero AE, Nicoletti F, Palumbo MA, Burrello N, Di Mauro M, Lunetta M, Bendtzen K and Cianci A (1998) Macrophage-derived cytokines in the follicular fluids of women with infertility due to immunological causes.

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Elevated levels of interleukin 6 and low levels of granulocyte-macrophage colony-stimulating factor. Cytokine 10,814–818.
Castro A, Castro O, Troncoso JL, Kohen P, Simon C, Vega M and Devoto L (1998) Luteal leukocytes are modulators of the steroidogenic process of human mid-luteal cells. Hum Reprod 13,1584–1589.
Chen HF, Shew JY, Chao KH, Chang LJ, Ho HN and Yang YS (2000) Luteinizing hormone up-regulates the expression of interleukin-1 beta mRNA in human granulosa-luteal cells. Am J Reprod Immunol 43,125–133.
Chen HL, Marcinkiewicz JL, Sancho-Tello M, Hunt JS and Terranova PF (1993) Tumor necrosis factor-alpha gene expression in mouse oocytes and follicular cells. Biol Reprod 48,707–714.
Chen TT, Lane TA, Doody MC and Caudle MR (1992) The effect of peritoneal macrophage-derived factor(s) on ovarian progesterone secretion and LH receptors: the role of calcium. Am J Reprod Immunol 28,43–50.
Christenson LK and Stouffer RL (1996) Isolation and culture of microvascular endothelial cells from the primate corpus luteum. Biol Reprod 55,1397–1404.
Cianci A, Calogero AE, Palumbo MA, Burrello N, Ciotta L, Palumbo G and Bernardini R (1996) Relationship between tumour necrosis factor alpha and sex steroid concentrations in the follicular fluid of women with immunological infertility. Hum Reprod 11,265–268.
Cohen PE, Nishimura K, Zhu L and Pollard JW (1999) Macrophages: important accessory cells for reproductive function. J Leukoc Biol 66,765–772.
Cohen PE, Zhu L, Nishimura K and Pollard JW (2002) Colony-stimulating factor 1 regulation of neuroendocrine pathways that control gonadal function in mice. Endocrinology 143,1413–1422.
Coulam, CB, Adamson SC and Annegers JF (1986) Incidence of premature ovarian failure. Obstet Gynecol 67,604–606.
Crosignani PG and Nicolosi AE (2001) Polycystic ovarian disease: heritability and heterogeneity. Hum Reprod Update 7,3–7.
Curry TE Jr and Osteen KG (2001) Cyclic changes in the matrix metalloproteinase system in the ovary and uterus. Biol Reprod 64,1285–1296.
Curry TE Jr, Song L and Wheeler SE (2001) Cellular localization of gelatinases and tissue inhibitors of metalloproteinases during follicular growth, ovulation, and early luteal formation in the rat. Biol Reprod 65,855–865.
Daeron M (1997) Fc receptor biology. Annu Rev Immunol 15,203–234.
Deshpande RR, Chang MY, Chapman JC and Michael SD (2000) Alteration of cytokine production in follicular cystic ovaries induced in mice by neonatal estradiol injection. Am J Reprod Immunol 44,80–88.
Devitt A, Moffatt OD, Raykundalia C, Capra JD, Simmons DL and Gregory CD (1998) Human CD14 mediates recognition and phagocytosis of apoptotic cells. Nature 392,505–509.
Dewerchin M, Nuffelen AV, Wallays G, Bouche A, Moons L, Carmeliet P, Mulligan RC and Collen D (1996) Generation and characterization of urokinase receptor-deficient mice. J Clin Invest 97,870–878.
Dhanasekaran N and Moudgal NR (1986) Studies on follicular atresia: role of tropic hormone and steroids in regulating cathepsin-D activity of preantral follicles of the immature rat. Mol Cell Endocrinol 44,77–84.
Dixit VD and Parvizi N (2001) Nitric oxide and the control of reproduction. Anim Reprod Sci 65,1–16.
Doody MC, WE Gibbons and VC Buttram, Jr (1988) Linear regression analysis of ultrasound follicular growth series: evidence for an abnormality of follicular growth in endometriosis patients. Fertil Steril 49,47–51.
Duggal PS, Ryan NK, Van der Hoek KH, Ritter LJ, Armstrong DT, Magoffin DA and Norman RJ (2002) Effects of leptin administration and feed restriction on thecal leucocytes in the preovulatory rat ovary and the effects of leptin on meiotic maturation, granulosa cell proliferation, steroid hormone and PGE2 release in cultured rat ovarian follicles. Reproduction 123,891–898.
Duncan WC (2000) The human corpus luteum: remodelling during luteolysis and maternal recognition of pregnancy. Rev Reprod 5,12–17.
Duncan WC, Rodger FE and Illingworth PJ (1998) The human corpus luteum: reduction in macrophages during simulated maternal recognition of pregnancy. Hum Reprod 13,2435–2442.
Erwig LP, Kluth DC, Walsh GM and Rees AJ (1998) Initial cytokine exposure determines function of macrophages and renders them unresponsive to other cytokines. J Immunol 161,1983–1988.
Espey LL (1980) Ovulation as an inflammatory reaction—a hypothesis. Biol Reprod 22,73–106.
Fasciani A, D'Ambrogio G, Bocci G, Monti M, Genazzani AR and Artini PG (2000) High concentrations of the vascular endothelial growth factor and interleukin-8 in ovarian endometriomata. Mol Hum Reprod 6,50–54.
Friedman A, Weiss S, Levy N and Meidan R (2000) Role of tumor necrosis factor alpha and its type I receptor in luteal regression: induction of programmed cell death in bovine corpus luteum-derived endothelial cells. Biol Reprod 63,1905–1912.
Fukumatsu Y, Katabuchi H, Naito M, Takeya M, Takahashi K and Okamura H (1992) Effect of macrophages on proliferation of granulosa cells in the ovary in rats. J Reprod Fertil 96,241–249.
Fukumatsu Y, Katabuchi H and Okamura H (1995) Immunohistochemical localization of epidermal growth factor and its effect on granulosa cell proliferation in rat ovary. Endocr J 42,467–473.
Garrido N, Navarro J, Remohi J, Simon C and Pellicer A (2000) Follicular hormonal environment and embryo quality in women with endometriosis. Hum Reprod Update 6,67–74.
Gaytan F, Morales C, Bellido C, Aguilar E and Sanchez-Criado JE (1998a) Ovarian follicle macrophages: is follicular atresia in the immature rat a macrophage-mediated event? Biol Reprod 58,52–59.
Gaytan F, Morales C, Garcia-Pardo L, Reymundo C, Bellido C and Sanchez-Criado JE (1998b) Macrophages, cell proliferation, and cell death in the human menstrual corpus luteum. Biol Reprod 59,417–425.
Geva E and Jaffe RB (2000) Role of vascular endothelial growth factor in ovarian physiology and pathology. Fertil Steril 74,429–438.
Gordon S (1999a) Macrophage-restricted molecules: role in differentiation and activation. Immunol Lett 65, 5–8.
Gordon S (1999b) Macrophages and the immune response. Fundamental Immunology. WE Paul. Philadelphia, Lippincott–Raven, pp 533–545.
Gudewicz PW, Frewin MB, Heinel LA and Minnear FL (1994) Priming of human monocyte superoxide production and arachidonic acid metabolism by adherence to collagen- and basement membrane-coated surfaces. J Leukoc Biol 55,423–429.
Hagglund AC, Ny A, Liu K and Ny T (1996) Coordinated and cell-specific induction of both physiological plasminogen activators creates functionally redundant mechanisms for plasmin formation during ovulation. Endocrinology 137,5671–5677.
Hagglund AC, Ny A, Leonardsson G and Ny T (1999) Regulation and localization of matrix metalloproteinases and tissue inhibitors of metalloproteinases in the mouse ovary during gonadotropin-induced ovulation. Endocrinology 140,4351–4358.
Hagglund AC, Basset P and Ny T (2001) Stromelysin-3 is induced in mouse ovarian follicles undergoing hormonally controlled apoptosis, but this metalloproteinase is not required for follicular atresia. Biol Reprod 64,457–463.
Hameed A, Fox WM, Kurman RJ, Hruban RH and Podack ER (1995) Perforin expression in human cell-mediated luteolysis. Int J Gynecol Pathol 14,151–157.
Hellberg P, Thomsen P, Janson PO and Brannstrom M (1991) Leukocyte supplementation increases the luteinizing hormone-induced ovulation rate in the in vitro-perfused rat ovary. Biol Reprod 44,791–797.
Hill JA, Welch WR, Faris HM and Anderson DJ (1990) Induction of class II major histocompatibility complex antigen expression in human granulosa cells by interferon gamma: a potential mechanism contributing to autoimmune ovarian failure. Am J Obstet Gynecol 162,534–540.
Hoek A, Schoemaker J and Drexhage HA (1997) Premature ovarian failure and ovarian autoimmunity. Endocr Rev 18,107–134.
Inaba K, Inaba M, Romani N, Aya H, Deguchi M, Ikehara S, Muramatsu S and Steinman RM (1992) Generation of large numbers of dendritic cells from mouse bone marrow cultures supplemented with granulocyte/macrophage colony-stimulating factor. J Exp Med 176,1693–1702.
Ingman WV and Robertson SA (2002) Defining the actions of transforming growth factor beta in reproduction. Bioessays 24,904–914.
Itoh M, Yano A, Li X, Miyamoto K and Takeuchi Y (1999) Limited uptake of foreign materials by resident macrophages in murine ovarian tissues. J Reprod Immunol 43,55–66.
Jasper M and Norman RJ (1995) Immunoactive interleukin-1 beta and tumour necrosis factor-alpha in thecal, stromal and granulosa cell cultures from normal and polycystic ovaries. Hum Reprod 10,1352–1354.
Jasper MJ, Robertson SA, Van der Hoek KH, Bonello N, Brannstrom M and Norman RJ (2000) Characterization of ovarian function in granulocyte-macrophage colony- stimulating factor-deficient mice. Biol Reprod 62,704–713.
Junttila I, Bourette RP, Rohrschneider LR and Silvennoinen O (2003) M-CSF induced differentiation of myeloid precursor cells involves activation of PKC-delta and expression of Pkare. J Leukoc Biol 73,281–288.

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Kaipia A, Chun SY, Eisenhauer K and Hsueh AJ (1996) Tumor necrosis factor-alpha and its second messenger, ceramide, stimulate apoptosis in cultured ovarian follicles. Endocrinology 137,4864–4870.

Kasuya K (1997) Elimination of apoptotic granulosa cells by intact granulosa cells and macrophages in atretic mature follicles of the guinea pig ovary. Arch Histol Cytol 60,175–184.

Katabuchi H, Fukumatsu Y, Araki M, Suenaga Y, Ohtake H and Okamura H (1996) Role of macrophages in ovarian follicular development. Horm Res 46,45–51.

Kelly CC, Lyall H, Petrie JR, Gould GW, Connell JM and Sattar N (2001) Low grade chronic inflammation in women with polycystic ovarian syndrome. J Clin Endocrinol Metab 86,2453–2455.

Kirsch TM, Friedman AC, Vogel RL and Flickinger GL (1981) Macrophages in corpora lutea of mice: characterization and effects on steroid secretion. Biol Reprod 25,629–638.

Kodelja V, Muller C, Tenorio S, Schebesch C, Orfanos CE and Goerdt S (1997) Differences in angiogenic potential of classically vs alternatively activated macrophages. Immunobiology 197,478–493.

Kohen P, Castro A, Caballero-Campo P, Castro O, Vega M, Makrigiannakis A, Simon C, Carvallo P and Devoto L (1999) Interleukin-1beta (IL-1beta) is a modulator of human luteal cell steroidogenesis: localization of the IL type I system in the corpus luteum. J Clin Endocrinol Metab 84,4239–4245.

Komatsu K, Manabe N, Kiso M, Shimabe M and Miyamoto H (2003) Changes in localization of immune cells and cytokines in corpora lutea during luteolysis in murine ovaries. J Exp Zool Part A Comp Exp Biol 296,152–159.

Kondo H, Maruo T and Mochizuki M (1995) Immunohistochemical evidence for the presence of tumor necrosis factor-alpha in the infant and adult human ovary. Endocr J 42,771–780.

Krakowski M, Abdelmalik R, Mocnik L, Krahl T and Sarvetnick N (2002) Granulocyte macrophage-colony stimulating factor (GM-CSF) recruits immune cells to the pancreas and delays STZ-induced diabetes. J Pathol 196,103–112.

Krusche CA, Vloet TD, Herrler A, Black S and Beier HM (2002) Functional and structural regression of the rabbit corpus luteum is associated with altered luteal immune cell phenotypes and cytokine expression patterns. Histochem Cell Biol 118,479–489.

Kudlow JE, Kobrin, MS, Purchio, AF, Twardzik, DR, Hernandez ER, Asa SL and Adashi EY (1987) Ovarian transforming growth factor-alpha gene expression: immunohistochemical localization to the theca-interstitial cells. Endocrinology 121,1577–1579.

Kuryszko J and Adamski RT (1987) Macrophages in atretic process of maturing ovarian follicles in mouse. Z Mikrosk Anat Forsch 101,212–220.

Lachapelle MH, Hemmings R, Roy DC, Falcone T and Miron P (1996) Flow cytometric evaluation of leukocyte subpopulations in the follicular fluids of infertile patients. Fertil Steril 65,1135–1140.

Lawler DF, Hopkins J and Watson ED (1999) Immune cell populations in the equine corpus luteum throughout the oestrous cycle and early pregnancy: an immunohistochemical and flow cytometric study. J Reprod Fertil 117,281–290.

Lee CH and Evans RM (2002) Peroxisome proliferator-activated receptor-gamma in macrophage lipid homeostasis. Trends Endocrinol Metab 13,331–335.

Lei ZM, Chegini N and Rao CV (1991) Quantitative cell composition of human and bovine corpora lutea from various reproductive states. Biol Reprod 44,1148–1156.

Leonardsson G, Peng XR, Liu K, Nordstrom L, Carmeliet P, Mulligan R, Collen D and Ny T (1995) Ovulation efficiency is reduced in mice that lack plasminogen activator gene function: functional redundancy among physiological plasminogen activators. Proc Natl Acad Sci USA 92,12446–12450.

Li XQ, Itoh M, Yano A, Xie Q, Miyamoto K and Takeuchi Y (1998) Distribution of F4/80-positive cells in developing ovaries in the mouse. Arch Histol Cytol 61,353–360.

Linehan SA, Martinez-Pomares L, Stahl PD and Gordon S (1999) Mannose receptor and its putative ligands in normal murine lymphoid and nonlymphoid organs: in situ expression of mannose receptor by selected macrophages, endothelial cells, perivascular microglia, and mesangial cells, but not dendritic cells. J Exp Med 189,1961–1972.

Long E, Huynh HT and Zhao X (1998) Involvement of insulin-like growth factor-1 and its binding proteins in proliferation and differentiation of murine bone marrow-derived macrophage precursors. Endocrine 9,185–192.

LoretdeMola JR, Flores JP, Baumgardner GP, Goldfarb JM, Gindlesperger V and Friedlander MA (1996) Elevated interleukin-6 levels in the ovarian hyperstimulation syndrome: ovarian immunohistochemical localization of interleukin-6 signal. Obstet Gynecol 87,581–587.

Loukides JA, Loy RA, Edwards R, Honig J, Visintin I and Polan ML (1990) Human follicular fluids contain tissue macrophages. J Clin Endocrinol Metab 71,1363–1367.

Loverro G, Maiorano E, Napoli A, Selvaggi L, Marra E and Perlino E (2001) Transforming growth factor-beta 1 and insulin-like growth factor-1 expression in ovarian endometriotic cysts: a preliminary study. Int J Mol Med 7,423–429.

Machelon V, Nome F, Durand-Gasselin I and Emilie D (1995) Macrophage and granulosa interleukin-1 beta mRNA in human ovulatory follicles. Hum Reprod 10,2198–2203.

Marcinkiewicz JL, Krishna A, Cheung CM and Terranova PF (1994) Oocytic tumor necrosis factor alpha: localization in the neonatal ovary and throughout follicular development in the adult rat. Biol Reprod 50,1251–1260.

Matsuyama S and Takahashi M (1995) Immunoreactive (ir)-transforming growth factor (TGF)-beta in rat corpus luteum: ir-TGF beta is expressed by luteal macrophages. Endocr J 42,203–217.

Mbikay M, Tadros H, Ishida N, Lerner CP, De Lamirande E, Chen A, El-Alfy M, Clermont Y, Seidah NG, Chretien M et al (1997) Impaired fertility in mice deficient for the testicular germ-cell protease PC4. Proc Natl Acad Sci USA 94,6842–6946.

McKnight AJ and Gordon S (1998) Membrane molecules as differentiation antigens of murine macrophages. Adv Immunol 68,271–314.

McKnight AJ, Macfarlane AJ, Dri P, Turley L, Willis AC and Gordon S (1996) Molecular cloning of F4/80, a murine macrophage-restricted cell surface glycoprotein with homology to the G-protein-linked transmembrane 7 hormone receptor family. J Biol Chem 271,486–489.

Mignot MH, Drexhage HA, Kleingeld M, Van de Plassche-Boers EM, Rao BR and Schoemaker J (1989) Premature ovarian failure II: Considerations of cellular immunity defects. Eur J Obstet Gynecol Reprod Biol 30,67–72.

Miller SC, Bowman BM and Rowland HG (1983) Structure, cytochemistry, endocytic activity, and immunoglobulin (Fc) receptors of rat testicular interstitial-tissue macrophages. Am J Anat 168,1–13.

Mizumoto H, Saito T, Ashihara K, Nishimura M, Takehara M, Tanaka R, Ito E and Kudo R (2002) Expression of matrix metalloproteinases in ovarian endometriomas: immunohistochemical study and enzyme immunoassay. Life Sci 71,259–273.

Monget P and Bondy C (2000) Importance of the IGF system in early folliculogenesis Mol Cell Endocrinol 163,89–93.

Monget P, Besnard N, Huet C, Pisselet C and Monniaux D (1996) Insulin-like growth factor-binding proteins and ovarian folliculogenesis. Horm Res 45,211–217.

Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M and Tapanainen JS (2003) Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88,4649–4654.

Murdoch WJ, Colgin DC and Ellis JA (1997) Role of tumor necrosis factor-alpha in the ovulatory mechanism of ewes. J Anim Sci 75,1601–1605.

Nagaoka I, Trapnell BC and Crystal RG (1990) Regulation of insulin-like growth factor I gene expression in the human macrophage-like cell line U937. J Clin Invest 85,448–455.

Nathan CF (1987) Secretory products of macrophages. J Clin Invest 79,319–326.

Newman SL and Tucci MA (1990) Regulation of human monocyte/macrophage function by extracellular matrix Adherence of monocytes to collagen matrices enhances phagocytosis of opsonized bacteria by activation of complement receptors and enhancement of Fc receptor function. J Clin Invest 86,703–714.

Nishimura K, Tanaka N, Ohshige A, Fukumatsu Y, Matsuura K and Okamura H (1995) Effects of macrophage colony-stimulating factor on folliculogenesis in gonadotrophin-primed immature rats. J Reprod Fertil 104,325–330.

Norman RJ (2001) Obesity, polycystic ovary syndrome and anovulation—how are they interrelated? Curr Opin Obstet Gynecol 13,323–327.

Norman RJ and Brannstrom M (1994) White cells and the ovary—incidental invaders or essential effectors? J Endocrinol 140,333–336.

Norman RJ and McVeigh E (1999) Polycystic ovary syndrome and implications for the menopause. Climacteric 2,141–143.

Ny T, Wahlberg P and Brandstrom IJ (2002) Matrix remodeling in the ovary: regulation and functional role of the plasminogen activator and matrix metalloproteinase systems. Mol Cell Endocrinol 187,29–38.

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Oksjoki S, Soderstrom M, Vuorio E and Anttila L (2001) Differential expression patterns of cathepsins B, H, K, L and S in the mouse ovary. Mol Hum Reprod 7,27–34.

Olive DL and Schwartz LB (1993) Endometriosis. N Engl J Med 328,1759–1769.

Olson KK, Anderson LE, Wiltbank MC and Townson DH (2001) Actions of prostaglandin F2alpha and prolactin on intercellular adhesion molecule-1 expression and monocyte/macrophage accumulation in the rat corpus luteum. Biol Reprod 64,890–897.

Oury F, Faucher C, Rives I, Bensaid M, Bouche G and Darbon JM (1992) Regulation of cyclic adenosine 3′,5′-monophosphate-dependent protein kinase activity and regulatory subunit RII beta content by basic fibroblast growth factor (bFGF) during granulosa cell differentiation: possible implication of protein kinase C in bFGF action. Biol Reprod 47,202–212.

Owen CA and Campbell EJ (1999a) The cell biology of leukocyte-mediated proteolysis. J Leukoc Biol 65,137–150.

Owen CA and Campbell EJ (1999b) Extracellular proteolysis: new paradigms for an old paradox. J Lab Clin Med 134,341–351.

Paavola LG (1979) The corpus luteum of the guinea pig IV Fine structure of macrophages during pregnancy and postpartum luteolysis, and the phagocytosis of luteal cells. Am J Anat 154,337–364.

Paavola LG and Boyd CO (1979) Surface morphology of macrophages in the regressing corpus luteum, as revealed by scanning electron microscopy. Anat Rec 195,659–681.

Parrott JA, Vigne JL, Chu BZ and Skinner MK (1994) Mesenchymal–epithelial interactions in the ovarian follicle involve keratinocyte and hepatocyte growth factor production by thecal cells and their action on granulosa cells. Endocrinology 135,569–575.

Pate JL and Landis Keyes P (2001) Immune cells in the corpus luteum: friends or foes? Reproduction 122,665–676.

Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J and Simon C (1998) The follicular and endocrine environment in women with endometriosis: local and systemic cytokine production. Fertil Steril 70,425–431.

Pellicer A, Albert C, Garrido N, Navarro J, Remohi J and Simon C (2000) The pathophysiology of endometriosis-associated infertility: follicular environment and embryo quality. J Reprod Fertil 55(Suppl),109–119.

Peterson CM, Hales HA, Hatasaka HH, Mitchell MD, Rittenhouse L and 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.

Petrovska M, Sedlak R, Nouza K, Presl J and Kinsky R (1992) Development and distribution of the white blood cells within various structures of the human menstrual corpus luteum examined using an image analysis system. Am J Reprod Immunol 28,77–80.

Petrovska M, Dimitrov DG and Michael SD (1996) Quantitative changes in macrophage distribution in normal mouse ovary over the course of the estrous cycle examined with an image analysis system. Am J Reprod Immunol 36,175–183.

Platt N, da Silva RP and Gordon S (1999) Class A scavenger receptors and the phagocytosis of apoptotic cells. Immunol Lett 65,15–19.

Rappolee DA, Mark D, Banda MJ and Werb Z (1988) Wound macrophages express TGF-alpha and other growth factors in vivo: analysis by mRNA phenotyping. Science 241,708–712.

Renier G, Clement I, Desfaits AC and Lambert A (1996) Direct stimulatory effect of insulin-like growth factor-I on monocyte and macrophage tumor necrosis factor-alpha production. Endocrinology 137,4611–4618.

Richards JS, Russell DL, Ochsner S, Hsieh M, Doyle KH, Falender AE, Lo YK and SC Sharma (2002) Novel signaling pathways that control ovarian follicular development, ovulation, and luteinization. Recent Prog Horm Res 57,195–220.

Ricke WA, Smith GW and Smith MF (2002) Matrix metalloproteinase expression and activity following prostaglandin F(2 alpha)-induced luteolysis. Biol Reprod 66,685–691.

Ross GD, Cain JA and Lachmann PJ (1985) Membrane complement receptor type three (CR3) has lectin-like properties analogous to bovine conglutinin as functions as a receptor for zymosan and rabbit erythrocytes as well as a receptor for iC3b. J Immunol 134,3307–3315.

Roy SK and Greenwald GS (1991) In vitro effects of epidermal growth factor, insulin-like growth factor-I, fibroblast growth factor, and follicle-stimulating hormone on hamster follicular deoxyribonucleic acid synthesis and steroidogenesis. Biol Reprod 44,889–896.

Saksela O, Hovi T and Vaheri A (1985) Urokinase-type plasminogen activator and its inhibitor secreted by cultured human monocyte-macrophages. J Cell Physiol 122,125–132.

Scurry JP, Hamand KA, Astley SB, Leake RE and Wells M (1994) Immunoreactivity of antibodies to epidermal growth factor, transforming growth factors alpha and beta, and epidermal growth factor receptor in the premenopausal ovary. Pathology 26,130–133.

Senturk LM, Seli E, Gutierrez LS, Mor G, Zeyneloglu HB and Arici A (1999) Monocyte chemotactic protein-1 expression in human corpus luteum. Mol Hum Reprod 5,697–702.

Serta RT and Seibel MM (1993) The influence of epidermal growth factor on progesterone production by human granulosa–luteal cells in culture. Hum Reprod 8,1005–1010.

Shakil T and Whitehead SA (1994) Inhibitory action of peritoneal macrophages on progesterone secretion from co-cultured rat granulosa cells. Biol Reprod 50,1183–1189.

Simon C, Frances A, Piquette G and Polan ML (1994a) Immunohistochemical localization of the interleukin-1 system in the mouse ovary during follicular growth, ovulation, and luteinization. Biol Reprod 50,449–457.

Simon C, Tsafriri A, Chun SY, Piquette GN, Dang W and Polan ML (1994b) Interleukin-1 receptor antagonist suppresses human chorionic gonadotropin-induced ovulation in the rat. Biol Reprod 51,662–667.

Skinner MK and Coffey RJ Jr (1988) Regulation of ovarian cell growth through the local production of transforming growth factor-alpha by theca cells. Endocrinology 123,2632–2638.

Skinner MK, Lobb D and Dorrington JH (1987) Ovarian thecal/interstitial cells produce an epidermal growth factor-like substance. Endocrinology 121,1892–1899.

Sprugel KH, McPherson JM, Clowes AW and Ross R (1987) Effects of growth factors in vivo. I. Cell ingrowth into porous subcutaneous chambers. Am J Pathol 129,601–613.

Sunderkotter C, Steinbrink K, Goebeler M, Bhardwaj R and Sorg C (1994) Macrophages and angiogenesis. J Leukoc Biol 55,410–422.

Tadros H, Chretien M and Mbikay M (2001) The testicular germ-cell protease PC4 is also expressed in macrophage-like cells of the ovary. J Reprod Immunol 49,133–152.

Takaya R, Fukaya T, Sasano H, Suzuki T, Tamura M and Yajima A (1997) Macrophages in normal cycling human ovaries; immunohistochemical localization and characterization. Hum Reprod 12,1508–1512.

Takehara Y, Dharmarajan AM, Kaufman G and Wallach EE (1994) Effect of interleukin-1 beta on ovulation in the in vitro perfused rabbit ovary. Endocrinology 134,1788–1793.

Tamura K, Tamura H, Kumasaka K, Miyajima A, Suga T and Kogo H (1998) Ovarian immune cells express granulocyte-macrophage colony-stimulating factor (GM-CSF) during follicular growth and luteinization in gonadotropin-primed immature rodents. Mol Cell Endocrinol 142,153–163.

Tamura M, Fukaya T, Enomoto A, Murakami T, Uehara S and Yajima A (1999) Transforming growth factor-beta isoforms and receptors in endometriotic cysts of the human ovary. Am J Reprod Immunol 42,160–167.

Tanaka N, Espey LL and Okamura H (1989) Increase in ovarian blood volume during ovulation in the gonadotropin-primed immature rat. Biol Reprod 40,762–768.

Terranova PF and Rice VM (1997) Review: cytokine involvement in ovarian processes. Am J Reprod Immunol 37,50–63.

Tilly JL, Billig H, Kowalski KI and Hsueh AJ (1992) Epidermal growth factor and basic fibroblast growth factor suppress the spontaneous onset of apoptosis in cultured rat ovarian granulosa cells and follicles by a tyrosine kinase-dependent mechanism. Mol Endocrinol 6,1942–1950.

Tontonoz P and Nagy L (1999) Regulation of macrophage gene expression by peroxisome-proliferator-activated receptor gamma: implications for cardiovascular disease. Curr Opin Lipidol 10,485–490.

Tozawa H, Brannstrom M, Petrucco O, Walker S, Chambers H, Pascoe V and Norman RJ (1995) Distribution of leukocyte subtypes in the sheep ovary after laser drilling. Hum Reprod 10,544–550.

Tsudo T, Harada T, Iwabe T, Tanikawa M, Nagano Y, Ito M, Taniguchi F and Terakawa N (2000) Altered gene expression and secretion of interleukin-6 in stromal cells derived from endometriotic tissues. Fertil Steril 73,205–211.

VanBlerkom J, Antczak M and Schrader R (1997) The developmental potential of the human oocyte is related to the dissolved oxygen content of follicular fluid: association with vascular endothelial growth factor levels and perifollicular blood flow characteristics. Hum Reprod 12,1047–1055.

VanderHoek KH, Maddocks S, Woodhouse CM, van Rooijen N, Robertson

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SA and Norman RJ (2000) Intrabursal injection of clodronate liposomes causes macrophage depletion and inhibits ovulation in the mouse ovary. Biol Reprod 62,1059–1066.

Vinatier D, Dufour P and Oosterlynck D (1996) Immunological aspects of endometriosis. Hum Reprod Update 2,371–384.

Wang LJ and Norman RJ (1992) Concentrations of immunoreactive interleukin-1 and interleukin-2 in human preovulatory follicular fluid. Hum Reprod 7,147–150.

Wang LJ, Brannstrom M, Robertson SA and Norman RJ (1992a) Tumor necrosis factor alpha in the human ovary: presence in follicular fluid and effects on cell proliferation and prostaglandin production. Fertil Steril 58,934–940.

Wang LJ, Pascoe V, Petrucco OM and Norman RJ (1992b) Distribution of leukocyte subpopulations in the human corpus luteum. Hum Reprod 7,197–202.

Wei RQ, Yee JB, Straus DC and Hutson JC (1988) Bactericidal activity of testicular macrophages. Biol Reprod 38,830–835.

Werb Z, Banda MJ and Jones PA (1980) Degradation of connective tissue matrices by macrophages I Proteolysis of elastin, glycoproteins, and collagen by proteinases isolated from macrophages. J Exp Med 152,1340–1357.

Wong KH, Negishi H and Adashi EY (2002) Expression, hormonal regulation, and cyclic variation of chemokines in the rat ovary: key determinants of the intraovarian residence of representatives of the white blood cell series. Endocrinology 143,784–791.

Yan G, Schoenfeld D, Penney C, Hurxthal K, Taylor AE and Faustman D (2000) Identification of premature ovarian failure patients with underlying autoimmunity. J Womens Health Gend Based Med 9,275–287.

Yan Z, Hunter V, Weed J, Hutchison S, Lyles R and Terranova P (1993) Tumor necrosis factor-alpha alters steroidogenesis and stimulates proliferation of human ovarian granulosal cells in vitro. Fertil Steril 59,332–338.

Yang XM and Park M (1995) Expression of the hepatocyte growth factor/scatter factor receptor tyrosine kinase is localized to epithelia in the adult mouse. Lab Invest 73,483–491.

Yoshimura Y, Santulli R, Atlas SJ, Fujii S and Wallach EE (1987) The effects of proteolytic enzymes on in vitro ovulation in the rabbit. Am J Obstet Gynecol 157,468–475.

Zhao Y, Burbach JA, Roby KF, Terranova PF and Brannian JD (1998) Macrophages are the major source of tumor necrosis factor alpha in the porcine corpus luteum. Biol Reprod 59,1385–1391.

Zolti M, Bider D, Seidman DS, Mashiach S and Ben-Rafael Z (1992) Cytokine levels in follicular fluid of polycystic ovaries in patients treated with dexamethasone. Fertil Steril 57,501–504.

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