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# THE POTENTIAL RELEVANCE OF CYTOKINES TO OVARIAN PHYSIOLOGY

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**Summary**—Elucidating the secrets of intraovarian intercellular communication constitutes a central area of investigation While most attention has been directed thus far at the somatic cellular components of the ovary, the potential role(s) and relative importance of the resident ovarian white blood cell have received relatively limited attention Efforts are currently under way to reconcile traditional ovarian physiology with observations relevant to intraovarian components of the white blood cell series In this connection, it is important to note that unlike some gonadal compartments, the ovary does not constitute an immunologically privileged site Thus, resident ovarian representatives of the white blood cell series can be observed at various stages of the ovarian life cycle Current concepts suggest that regulatory cellular networks formerly viewed in immune terms now fall within the broad domain of endocrinology Viewed in this light, resident ovarian representatives of the white blood cell series may constitute potential *in situ* modulators of ovarian function acting in all likelihood through the local secretion of regulatory cytokines As the flow of information is probably multi directional, the very same cells are probably targeted for steroidal and peptidergic input in keeping with the existence of multiple autocrine and paracrine loops

Unlike some gonadal compartments (e g the testicular seminiferous tubule), the ovary does not constitute an immunologically privileged site Thus, resident ovarian (i e extravascular) mononuclear phagocytes (macrophages), lymphocytes and polymorphonuclear granulocytes can be observed at various stages of the ovarian life cycle For example, macrophages (Fig 1), but not other representatives of the white blood cell series, are now known to constitute a major cellular component of the interstitial (i.e. interfollicular) ovarian compartment [1] In part, these macrophages are present within the ovarian stroma near perifollicular capillaries [2] Unfortunately, little is known at this time as regards this apparently permanent (i e non-cyclic) presence The above notwithstanding, it is tempting to speculate that interstitial macrophages could exert paracrine effects at the level of adjacent somatic ovarian cells with which they have been observed to establish physical contact [1], perhaps through adhesion-promoting receptors [3]

With the exception of macrophage, few if any other white blood cells have been observed in the early phases of follicular development However, this status quo is precipitously altered as preovulatory events (or atresia) prompt massive ovarian infiltration by several representatives of the white blood cell series [4]. Paving the way are mast cells [5–10] the relative representation of which increases progressively during the latter portion of the follicular phase, an invasion culminated with their degranulation in response to the proestrous LH surge [11] The resultant follicular hyperemia [12–16], coupled with chemotactic signalling [17, 18] appear to not only play a critical role in subsequent luteal function [19] but also herald an orderly sequence of events reminiscent of an acute inflammatory response [20] The follicular hyperemia observed appears to be initiated by histamine [21–25] and propagated by prostaglandin ($E_2$) Both agents cause vasodilatation and enhanced capillary/venule permeability by relaxing vascular smooth muscle The released histamine was found without effect on bovine luteal steroidogenesis [26] while stimulating murine follicular progesterone accumulation [27] However, the precise significance of this latter observation remains uncertain

Next to arrive are eosinophils and T lymphocytes which migrate into the corpus luteum [28]. Interestingly, ovine corpora lutea have been shown to secrete a specific chemoattractant for eosinophils [18, 29] the precise nature of which

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has not been identified However, increased numbers of eosinophils have been observed in corpora lutea of sheep treated with a luteolytic dose of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) [29] Conceivably then, the chemoattractant could be $PGF_{2\alpha}$-inducible [20] Interestingly, infiltration and subsequent degranulation of these cells has been reported to occur before evidence of either functional or structural luteal regression [29] It has therefore been suggested that cytotoxins released by eosinophils could injure luteal cells, cause physical changes in membranes, and/or activate degradation of mRNA, thereby resulting in luteal demis [28] Moreover, unmasking of cellular antigens by removal of sialic acid residues and/or exposure by a change in the physical state of the cellular membrane could lead to an antibody-mediated reaction involving complement, cellular destruction, and phagocytosis [28]

Activated T cells are known to produce lymphokines that attract and activate monocytes/macrophages Accordingly, T lymphocyte are followed in short sequence by phagocytic monocytes with ultrastructural, histochemical, and functional features indistinguishable from those of observed in other body sites [30] These attributes include intense staining for nonspecific esterase activity, phagocytosis of IgG-coated red blood cells via an Fc receptor, ingestion of latex beads, and trypsin-resistance (as assessed by adherence to the surface of culture dishes) Furthermore, ovarian macrophages have been shown to specifically bind to their surface a monoclonal antibody against a plasma membrane protein of mononuclear phagocytes Macrophages within the pericapillary spaces represent, in all likelihood, the dark stellate "K" cells that have been scattered among the granulosa cells in light macrophages [31] In this connection, it appears worthy of note that co-cultures of ovarian macrophages and luteal cells were seen to make discrete cell–cell contacts [30] This *in vitro* phenomenon may in fact be analogous to the relationship observed *in-vivo* wherein macrophages have been observed to send out processes contacting several adjacent luteal cells raising the possibility of cell–cell signalling [32] Yet other, phagocytically-active macrophages, highly represented in older (regressing) but not young corpora lutea, appear to be involved in heterophagy of structurally-damaged luteal cells resulting from the structural disintegration of the corpus luteum [33] As the corpus luteum matures, these macrophages are characterized by the presence of many electron-dense lysosomal granules and phagocytotic granules of variable configuration and structure throughout their cytoplasm [34] Of note, the invasion of macrophages and T lymphocytes into the corpus luteum is delayed by pregnancy and thus is not strictly a function of age of the corpus luteum Indeed, only a few macrophages and T lymphocytes were observed in rabbit corpora lutea on day 19 of pregnancy whereas the numbers of these cells were 6- to 8-fold higher in corpora lutea on day 19 of pseudopregnancy By the day of parturition, however, macrophages do begin to infiltrate the corpora lutea of pregnancy [35]

Although macrophages have been observed as a prominent cell type within the corpus luteum of several species [31–42], little attention has been given to the properties and role of these cells The only role previously considered has been heterophagy of damaged luteal cells That resident macrophages may function as potential *in situ* regulators of ovarian function has been suggested, at least in part, by the finding of numerous macrophages in regressing corpora luteum while only a few were observed in their young counterparts Moreover, regressing (but not young) corpora lutea readily produced tumor necrosis factor $\alpha$ (TNF$\alpha$) [35, 43] in response to *in vitro* stimulation with lipopolysaccharide (LPS) The latter antigen is the cell–wall component of gram-negative bacteria which is a potent stimulus for TNF production by macrophages Although the mechanism(s) whereby macrophages influence ovarian function (rather than structure) remain uncertain, it is generally presumed that local paracrine secretion of regulatory molecule(s) (i e cytokines) may be at play

The potential relevance of macrophages becomes immediately evident when consideration is being given to their ability to elaborate several growth factors previously implicated as putative intraovarian regulators [44, 45] Indeed, non-cytokine secretory products of the macrophage such as basic fibroblast growth factor [46–61], transforming growth factor (TGF)$\alpha$ [47, 51, 52, 55, 59–68], and TGF$\beta$1 [69–82] have been shown to exert profound modulatory effects on the growth and functional development of the ovarian granulosa/luteal cell More recently however, increasing attention has been paid to the potential role of macrophage-generated cytokines the relevance of which to ovarian physiology is the subject of current investigation

Interleukin-1 (IL-1), a polypeptide cytokine (previously referred to as lymphocyte activating factor) predominantly produced and secreted by activated macrophages, has been shown to possess a wide range of biological functions as well as to play a role as an immune mediator [83–85] At the level of the ovary, IL-1 has recently been observed to suppress the functional and morphological luteinization of cultured murine and porcine granulosa cells [86–91] Exerted at "physiologic" ($10^{-9}$ M) concentrations, IL-1 action could not be attributed to altered cell viability Rather, the anti-gonadotropic activity of IL-1 appeared to involve site(s) of action both proximal and distal to cAMP generation According to Fukuoka *et al* [90] the ability of IL-1 to inhibit granulosa cell differentiation is strongly (and if fact inversely) associated with its ability to promote granulosa cell growth Indeed, non-dividing fully differentiated highly luteinized granulosa cells no longer appear to respond to IL-1 Accordingly, it has been suggested that the effects of IL-1 at the level of the granulosa cell may depend on the proliferative status of this cell type More recent work by Kasson and Gorospe [91] sheds additional light on the ovarian relevance of interleukins Indeed, both IL-1$\alpha$ and -1$\beta$ augmented the FSH-stimulated accumulation of 20$\alpha$-dihydroprogesterone In all cases, less IL-1$\beta$ than -1$\alpha$ was required to produce a comparable affect IL-2 slightly, but significantly, enhanced both FSH-stimulated progesterone and 20$\alpha$-dihydroprogesterone production but had no effect on FSH-stimulated estrogen production of LH/hCG receptor induction IL-3 potentiated the 20$\alpha$-dihydroprogesterone response to FSH by up to 65% but had no effect on FSH-stimulated progesterone or estrogen production or LH/hCG receptor induction More recent preliminary studies (Hurwitz and Adashi, unpublished) suggest that the theca-interstitial cell may also be a site of IL-1 (but not IL-2) reception and action

Interestingly, the circulating levels of IL-1 have been observed to be elevated during the luteal (but not preovulatory) phase of normally cycling women [92] The possible role of progesterone in this regard is supported by the observation that IL-1 activity in human pelvic macrophages is subject to hormonal regulation by gonadal steroids [93] Specifically, low concentrations of progesterone appear to upregulate macrophage IL-1 gene expression [94] In contrast, higher concentrations of progesterone significantly inhibit IL-1 activity [94]

Although the relevance of IL-1 to ovarian physiology remains a matter of study, it is tempting to speculate that IL-1 could possibly be the elusive intraovarian luteinization-inhibitor, the putative suppressor of premature follicular luteinization Such speculation appears particularly intriguing in light of the apparent progesterone-dependence of IL-1 gene expression [94] While much remains to be learned on the intraovarian cellular origin of IL-1, resident interstitial ovarian macrophages could well be a site of hormonally-regulated IL-1 gene expression given the reported gonadotropin-dependence of their testicular counterparts [95–97] IL-1 could also be produced by ovarian cell(s) proper as has been shown for various other specialized cell types [85] Interestingly, significant amounts of IL-1-like activity have been detected in human follicular fluid [98, 99]

While the rudimentary nature of current observations is clearly apparent, there is every reason to believe that continued investigation will provide new and meaningful insight relevant to the understanding of the complex interactions between the various cellular components of the ovary Now that the necessary tools are available, additional efforts in this area are to be anticipated If progress to date is an indication, odds are that the next decade will reveal the resident ovarian white blood cell and its cytokine messengers to play major roles throughout the ovarian life cycle

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