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MINIREVIEW

Immunologically Relevant Cells in the Uterus[1]

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ABSTRACT

Macrophages and a special subset of lymphocyte natural killer (NK) cells populate the uteri of cycling humans, mice, and rats. After implantation, major changes take place that have important functional implications. The macrophages and NK cells increase in number, are redistributed into specific uterine compartments, and exhibit markers consistent with cell activation. Activation enhances macrophage and NK cell production of a wide range of pleiotropic, multifunctional polypeptide growth factors, reactive oxygen intermediates, and bioactive lipids. Thus, activated uterine hematopoietic cells are equipped to perform certain immunological and nonimmunological functions within their microenvironments that could have major influences on the course of pregnancy.

INTRODUCTION

Bone marrow-derived cells best known for their roles in immune responses, i.e., macrophages and lymphocytes, are common inhabitants of mammalian uteri. Other types of bone marrow-derived cells—notably neutrophils, eosinophils, mucosal lymphocytes bearing T-cell receptors of the γ/δ type, and serosa-type mast cells—are present under certain conditions. Their potential contribution to resistance to infection and inflammatory conditions associated with mating and pregnancy should not be overlooked.

The present discussion will focus on macrophages and lymphocytes populating mouse, rat, and human uteri, with emphasis on recent investigations that have provided some enlightenment on their potential functions. In humans and in these murids, placentation is similar and extensive experimentation relating to the present topic has been done. Interested readers are referred to more extensive commentaries on uterine hematopoietic cells [1–6].

Distribution of Hematopoietic Cells in Cycling Uteri

Macrophages in human, rat, and mouse uteri are distributed throughout the endometrial stroma and myometrial connective tissue (Fig. 1A). In mice, macrophages identified with a monoclonal antibody, F4/80, may be observed encircling the endometrial glands and infiltrating the luminal epithelium at late estrus to diestrus [7]. Myometrial macrophages are often larger in size than endometrial macrophages and frequently reside immediately beneath the uterine serosa.

Lymphoid aggregates containing both helper (CD4+) and cytotoxic/suppressor (CD8+) subsets of T lymphocytes as well as antibody-producing B lymphocytes are common in human endometrium [8]. Lymphocytes constituting another subset, first called stromal granulocytes but now termed large granular lymphocytes (LGL) [9], are present in large numbers and are maintained in the tissue by ovarian steroid hormones [10]. Accumulations of antigen-specific lymphoid cells are less evident in cycling murid uteri than in human uteri, whereas many lymphocytes resembling the human LGL are present in the mouse [11]. Mouse LGL are randomly distributed through the endometrium and myometrium, where they are identified with a monoclonal antibody (LGL-1) as early as 2 wk of age. The onset of puberty has no effect on LGL distribution or density [11].

Distribution of Hematopoietic Cells during Pregnancy

A dramatic redistribution of uterine macrophages takes place immediately after implantation. Macrophages flee from the implantation site, a phenomenon first reported in rats by Tachi and Tachi [12]. A similar situation occurs in mice, where F4/80+ cells are scarce at the implantation site [13] and are entirely absent from the primary decidua [14]. In both mice and rats, macrophages continue to be excluded from the primary decidua and decidua basalis as pregnancy progresses to term [14, 15], although some monocytes/macrophages are present in fibrin and maternal blood near the placenta. Redline and Lu have presented a reasonable explanation for this interesting observation [16]. They found that mouse macrophages do not migrate well on decidual substratum. Throughout the balance of mouse and rat pregnancy, macrophages are relegated to compartments distant from the placenta, the secondary decidua immediately beneath the circular muscle, the metrial gland, and the myometrium (Fig. 1B).

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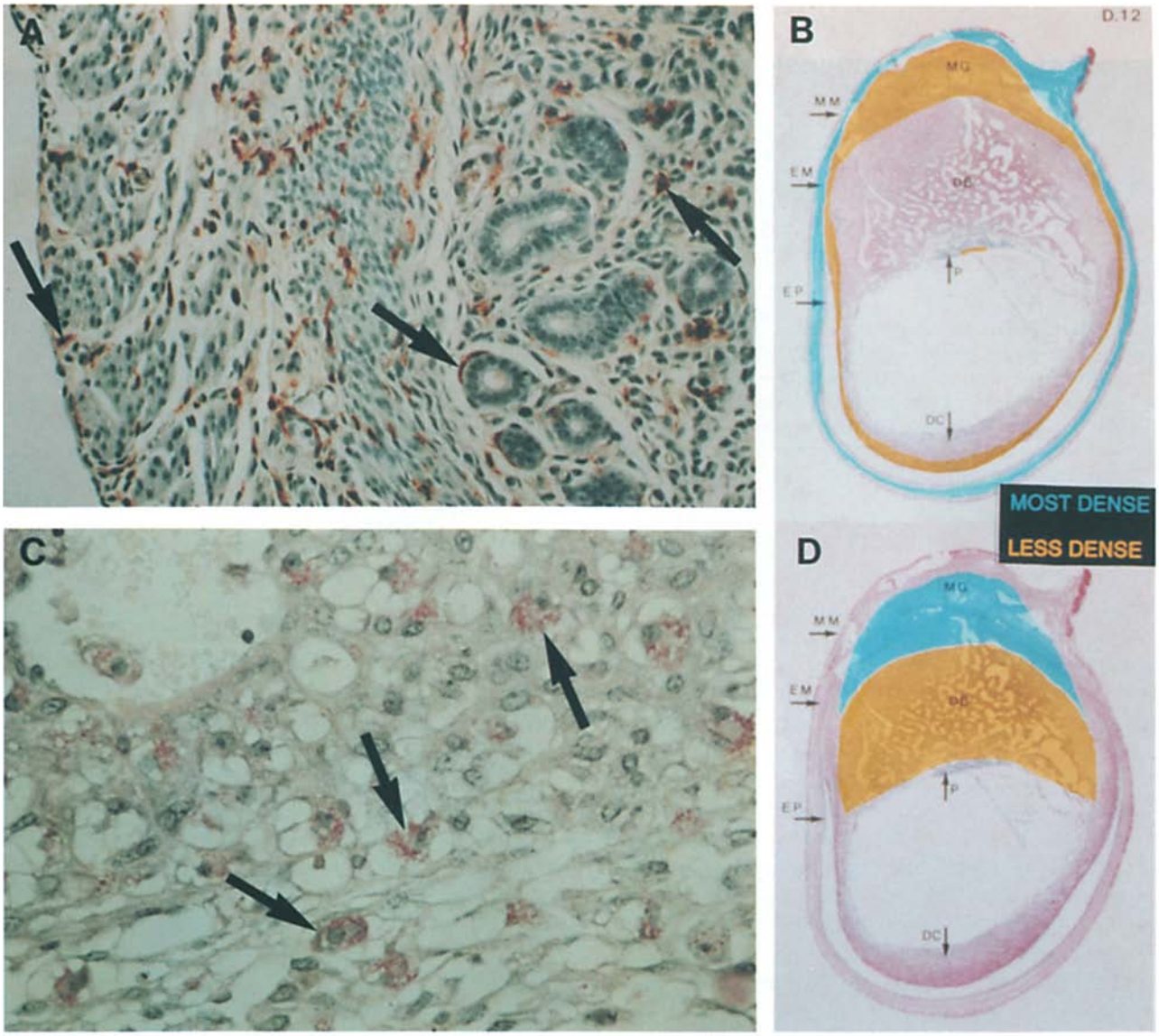

FIG. 1. Macrophages and NK-like cells in murid uteri. A) Identification of macrophages in cycling mouse uterus with the monoclonal antibody F4/80 (arrows). In diestrous uterus, macrophages are distributed throughout the endometrial stroma and encircle the endometrial glands (right side). F4/80+ cells are located in the connective tissue surrounding bundles of longitudinal and circular muscle in the myometrium (left side). Original magnification ×100. B) Distribution of macrophages in Day 12 rat uterus. C) Large NK-like cells in Day 15 rat metrial gland (arrows) contain prominent intracellular granules. The tissue section was stained to reveal glycogen. Original magnification ×400. D) Distribution of NK-like cells in Day 12 rat uterus. In (B) and (D), blue shading indicates areas of high density and yellow shading indicates areas of lesser density of each type of cell. A fragment of the placenta in shown; the embryo has been removed. DB, decidua basalis; DC, decidua capsularis; EM, undecidualized endometrium; EP, luminal epithelium; MG, metrial gland; MM, myometrium; P, placenta.

Uterine lymphocytes are also redistributed. This has been clearly illustrated in studies on rat and mouse uteri, where the majority of LGL are relocated into the metrial gland and decidua (Fig. 1D). These cells, originally termed granulated metrial gland (GMG) cells because of their distinct intracellular granules (Fig. 1C), arise from bone marrow LGL precursors [17]. As the cells mature during pregnancy, the LGL marker is lost and mature GMG exhibit markers consistent with their identification as natural killer (NK) cells such as Thy-1, NK1.1, and asialo-GM1 [18–20]. Studies on the lineage of these cells using immune-deficient mouse strains such as *scid* and *bg* demonstrate clearly that the uterine lymphocytes are not derived from the T lineage but are also not classical NK cells [21]. Even though the exact nature of these cells remains a matter of some debate because the uterine NK-like cells fail to lyse normal NK cell targets [22], they appear more closely related to NK cells than to any other lineage and are, therefore, referred to hereafter as NK-like cells. Unlike macrophages, uterine NK-like cells migrate in significant numbers into the primary

decidua of murids and are found deep in the labyrinthine region of the placenta. Human LGL are particularly abundant in first-trimester decidua [23]. Human lymphocytes are also related to the NK cell lineage but do not display the same markers as the majority of blood NK cells. While uterine NK-like cells bind antibodies to CD56, they fail to bind antibodies to CD16 [24]. Thus, a specific subset of blood NK cells is selected into the uterus.

Interestingly, mouse and rat GMG are abundant from the middle to the late stages of gestation, whereas the numbers of human uterine LGL decrease after the first trimester of pregnancy. Whether or not this might simply reflect the longer period of gestation in humans is not known.

Chemoattraction

Uterine macrophages increase in density during mouse pregnancy [25]. In immature rat uteri, this influx is related to stimulation by estrogens, which promote migration of macrophages, eosinophils, and CD4+ helper T lymphocytes but not CD8+ cytotoxic/suppressor T lymphocytes or NK-like cell populations [26]. Female sex steroid hormones enhance uterine epithelial cell production of polypeptide growth factors that are chemotactic for monocytes: colony-stimulating factor-1 (CSF-1) [27, 28], transforming growth factor-β (TGF-β) [29, 30], granulocyte-monocyte colony-stimulating factor (GM-CSF) [31, 32], and tumor necrosis factor-α (TNF) (K.F. Roby and J.S. Hunt, unreported data; [33]). These might then act as second messengers.

Studies utilizing osteopetrotic (*op/op*) mice, a natural mutant strain with a defective CSF-1 gene [34], have eliminated maternal CSF-1 as the sole chemoattractant for macrophages [14]. *Op/op* mice have few blood monocytes and low levels of tissue macrophages because CSF-1 is required for the differentiation of bone marrow stem cells into this lineage. Macrophages are entirely absent from the uteri of cycling *op/op* mice; yet by gestation Day 7, their uteri contain approximately half the macrophage component of heterozygous CSF-1-competent *+/op* mice [14]. GM-CSF gene expression in uterine epithelial cells is stimulated immediately after mating by seminal fluid and is also governed by estrogens [31, 32]. Thus, GM-CSF may well be the major macrophage chemoattractant. Experiments on transgenic mice deficient in other cytokines [35, 36] could be highly informative.

Potential chemoattractants for uterine NK-like cells are as yet unidentified, but they clearly do not include CSF-1; the proportions of these cells are unaltered in *op/op* mice [37]. Unlike macrophages, the NK-like cells are not particularly attracted to uterine epithelium; this suggests that GM-CSF, TNF, and TGF-β1 also may not be major chemoattractants for this lineage.

Differentiation

Upon arrival in the uterus, blood monocytes differentiate into tissue macrophages. Studies on rat uteri using two monoclonal antibodies that bind to monocytes (ED1) and differentiated macrophages (ED2) have shown that both subpopulations are present in pregnant uteri [38]. ED1+ cells are more common near blood vessels in the metrial gland, and ED2+ cells predominate in the myometrium, where their density relative to other types of cells peaks at midgestation. CSF-1 is critical to differentiation of mouse uterine macrophages. In the *op/op* mouse uterus the cells remain small and rounded, whereas in that of the *+/op* mouse they spread in a normal manner [14].

Differentiation-inducing factors for uterine NK-like cells are not clearly defined. The NK-like cells increase in size during pregnancy and develop prominent intracellular granules (Fig. 1C), indicating that unidentified pregnancy-associated factors exert a strong influence on this lineage. Interestingly, progesterone is important, while the presence of the embryo is not [39]. Nor is CSF-1 involved; NK-like cells develop normally in *op/op* mice [37].

Priming and Activation

During pregnancy, both macrophages and NK-like cells in the uterus exhibit markers associated with priming and activation for specific functions such as presentation of antigens and killing of tumor cells. Many more macrophages in pregnant than in cycling mouse uteri express major histocompatibility class II (Ia) antigens [25], and mouse NK-like cells gradually develop the NK cell activation markers perforin and serine esterases [19]. This is a critical step; activated hematopoietic cells are more efficient eliminators of microorganisms and aberrant cells and produce significantly higher levels of polypeptides, oxygen intermediates, and bioactive lipids.

Recent studies in our laboratory suggest that interferon-γ (IFN-γ) may be instrumental in promoting activation of uterine hematopoietic cells. IFN-γ acts as a "priming" agent, preparing macrophages and NK-like cells for heightened responses. While receptors for IFN-γ (IFN-γR) are comparatively low in endometrial stromal cells in the uteri of cycling mice, myometrial macrophages develop high levels of IFN-γR mRNA and protein by Day 7 and receptor expression develops in NK-like cells by Day 9 [7]. It seems reasonable to assume that increased receptor expression will enhance receptivity to IFN-γ and that the cells will be primed subsequent to receptor/ligand interactions. While a local source of IFN-γ has not yet been identified in mice, IFN-γ mRNA is present in first-trimester human placental cytotrophoblast cells [40] and in pig trophoblast [41]. Hence, signals emanating from the placenta might stimulate resident hematopoietic cells. Potential placental stimulatory molecules are not limited to IFN-γ. Parr and coworkers [42] have proposed that uterine NK-like cells might possibly be activated via prolactin receptors and/or the p75 component of the interleukin (IL)-2 receptor by placental lactogens. This has not been evaluated experimentally.

Functions of Uterine Macrophages and Lymphocytes

Multiple functions have been postulated for uterine hematopoietic cells (Table 1). These include immunological as well as nonimmunological activities. In the first category, uterine macrophages bearing Ia antigens might present processed exogenous molecules to lymphocytes, a first step in the development of humoral and cellular immune responses. However, classical T helper (CD4+) lymphocytes are uncommon in the uterus during pregnancy [25, 43]. Resident uterine hematopoietic cells are likely to contribute to the exclusion of antigen-specific CD4+ lymphocytes, a condition believed to facilitate semiallogeneic pregnancy [44]. Mouse uterine macrophages produce high levels of prostaglandin E_2 [45, 46]; and in both rats and mice, macrophages and NK-like cells transcribe the TGF-β1 gene [47]. Prostaglandin E_2 and TGF-β1 are well-described inhibitors of lymphocyte proliferation. Clark and coworkers [48] have reported extensively on a comparatively uncommon small uterine lymphocyte-like cell producing a TGF-β2-like substance with similar inhibitory properties.

Uterine macrophages and NK-like cells are likely to protect the embryo against infections; in other contexts, both lineages kill bacteria and viruses. Studies by Tachi and Tachi [13] first showed that uterine macrophages are phagocytic in situ, and this was confirmed by Redline and Lu [49]. While the burden of protecting against transmission is likely to fall on the NK-like cells because of the dearth of macrophages in the decidua, placental macrophages are phagocytic and might therefore supplement the activities of maternal cells.

With regard to nonimmunological functions, both macrophages and NK-like cells have been postulated to prevent tumor-like invasive trophoblast cells from overwhelming maternal tissues [1–6]. Studies on the distribution of the two lineages show that NK-like cells are better positioned for this critical activity, and studies by Stewart and Mukhtar [50] have shown that the NK-like cells do indeed lyse mouse trophoblast cells. Myometrial macrophages and NK-like cells in the metrial gland transcribe the genes coding for two cytokines that have been shown to inhibit rat trophoblast cell DNA synthesis [51], TNF and TGF-β1 ([38, 47, 52]; E.L. Parr, H.-L. Chen, M.B. Parr, and J.S. Hunt, unpublished results).

Interestingly, anatomic location relative to the placenta seems to influence the pattern of cytokines synthesized by macrophages. Neither fetal macrophages within human first-trimester placental villi nor maternal macrophages in placenta-associated fibrin contain TNF gene products [53]. Instead, these cells contain IL-1β [54], a cytokine that has been shown to enhance rat trophoblast cell proliferation [51]. These observations support the concept of functional compartmentalization and raise intriguing questions regarding local influences on uterine macrophages.

Potential influences of macrophages on myometrial function remain almost entirely uninvestigated. The myometrium is the favored location of macrophages during pregnancy, and these versatile cells produce many proteases, such as collagenase and elastase [55], that could facilitate tissue remodeling required for accommodation of the growing embryo. Recent studies in our laboratory show that uterine macrophage-like cells contain the inducible form of nitric oxide synthase (J. Huang and J.S. Hunt, unreported data). Thus nitric oxide, which maintains muscle relaxation, might be an important product of these cells that could be synthesized as required for specific stages of pregnancy.

TABLE 1. Potential and described functions of uterine hematopoietic cells during pregnancy.[a]

	Macrophages	NK-like cells
Immunological		
Antigen presentation	+	0
Protection against infection	+++	+++
Immunosuppression	+++	+
Nonimmunological		
Protection against trophoblast invasion	++	+++
Cytokine mRNA and/or protein synthesis		
IL-1β	+++	0
TNF	+++	+++
TGF-β1	+++	+++
Modulation of myometrial function	++	0

[a]0, unlikely; +, possible; ++, probable; +++, certain.

PERSPECTIVES

Considerable progress has been made in clarifying the roles of macrophages and NK-like cells during pregnancy through the application of immunocytochemical and molecular biological techniques. An important new principle that has emerged from these investigations is that hematopoietic cells are not the sole source of growth-, differentiation-, and inflammation-associated cytokines. Uterine epithelial cells produce CSF-1, TGF-β, TNF, GM-CSF, and IL-6 (reviewed in [56, 57]); and placental trophoblast cells also synthesize a broad spectrum of polypeptide growth factors [40, 53].

Yet contributions from hematopoietic cells may be critical, particularly during infections [1, 58]. It is a unique feature of these cells that their genes coding for specific effector molecules are inducible by the combination of IFN-γ and endotoxin from Gram-negative bacterial walls. After exposure to these activating agents, macrophages and NK cells produce markedly higher levels of growth factors, reactive oxygen intermediates, and bioactive lipids than do other types of cells. Hence, the extraordinarily high levels of these substances found in amniotic fluids during infection-associated preterm labor [59–62] probably originate primarily in hematopoietic cells; this hypothesis is under exploration in several laboratories.

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REFERENCES

1. Hunt JS. Cytokine networks in the uteroplacental unit: macrophages as pivotal regulatory cells. J Reprod Immunol 1989; 16:1–17.
2. Hunt JS. The role of macrophages in the uterine response to pregnancy. Placenta 1990; 11:467–475.
3. Hunt JS, Pollard JW. Macrophages in the uterus and placenta. In: Gordon S, Russell SW (eds.), Current Topics in Microbiology and Immunology. Macrophages and Macrophage Activation. Berlin-Heidelberg: Springer-Verlag, 1992: 36–63.
4. Croy BA. Granulated metrial gland cells—interesting cells found in the pregnant uterus. Am J Reprod Immunol 1990; 23:19–21.
5. King A, Loke YW. Uterine large granular lymphocytes: a possible role in embryonic implantation? Am J Obstet Gynecol 1990; 162:308–310.
6. Stewart IJ. Granulated metrial gland cells in the mouse placenta. Placenta 1990; 11:263–275.
7. Chen H-L, Kamath R, Pace JL, Russell SW, Hunt JS. Gestation-related expression of the interferon-γ receptor gene in mouse uterine and embryonic hematopoietic cells. J Leukocyte Biol (in press).
8. Khong TY. Immunohistologic study of the leukocytic infiltrate in maternal uterine tissues in normal and preeclamptic pregnancies at term. Am J Reprod Immunol 1987; 15:1–8.
9. Bulmer JN, Hollings D, Ritson A. Immunocytochemical evidence that endometrial stromal granulocytes are granulated lymphocytes. J Pathol 1987; 153:281–288.
10. King A, Wellings V, Gardner L, Loke YW. Immunocytochemical characterization of the unusual large granular lymphocytes in human endometrium throughout the menstrual cycle. Human Immunol 1989; 24:195–205.
11. Kiso Y, McBey B-A, Mason L, Croy BA. Histological assessment of the mouse uterus from birth to puberty for the appearance of LGL-1+ natural killer cells. Biol Reprod 1992; 47:227–232.
12. Tachi C, Tachi S, Knyszynski A, Linder HR. Possible involvement of macrophages in embryo-maternal relationships during ovum implantation in the rat. J Exp Zool 1981; 217:81–92.
13. Brandon JM. Leucocyte distribution in the uterus during the preimplantation period of pregnancy and phagocyte recruitment to sites of blastocyst attachment in mice. J Reprod Fertil 1993; 98:567–576.
14. Pollard JW, Hunt JS, Wiktor-Jedrzejczak W, Stanley ER. A pregnancy defect in the osteopetrotic (*op/op*) mouse demonstrates the requirement for CSF-1 in female fertility. Dev Biol 1991; 148:273–283.
15. Redline RW, Lu CY. Localization of fetal major histocompatibility complex antigens and maternal leukocytes in murine placenta. Lab Invest 1989; 61:27–36.
16. Redline RW, McKay DB, Vazquez MA, Papaioannou VE, Lu CY. Macrophage functions are regulated by the substratum of murine decidual stromal cells. J Clin Invest 1990; 85:1951–1958.
17. Peel S, Steward IJ, Bulmer D. Experimental evidence for the bone marrow origin of granulated metrial gland cells of the mouse uterus. Cell Tissue Res 1983; 233:647–656.
18. Parr EL, Parr MB, Young JDE. Localization of a pore-forming protein (perforin) to granulated metrial gland cells. Biol Reprod 1987; 37:1327–1336.
19. Parr EL, Young LHY, Parr MB, Young JD-E. Granulated metrial gland cells of pregnant mouse uterus are natural killer-like cells that contain perforin and serine esterases. J Immunol 1990; 145:2365–2372.
20. Linnemeyer PA, Pollack SB. Murine granulated metrial gland cells at uterine implantation sites are natural killer lineage cells. J Immunol 1991; 147:2530–2531.
21. Croy, BA, Chapeau C, Reed N, Stewart IJ, Peel S. Is there an essential requirement for bone-marrow-derived cells at the fetomaternal interface during successful pregnancy? A study of pregnancies in immunodeficient mice. In: Wegmann TG, Gill III TJ, Nisbet-Brown E (eds.), Molecular and Cellular Immunobiology of the Maternal Fetal Interface. New York: Oxford University Press, 1991: 168–188.
22. Stewart IJ, Peel S. Mouse metrial gland cells do not kill Yac-1 myeloma cells. J Reprod Immunol 1993; 24:165–171.
23. Kabawat SE, Mostoufi-Zadeh M, Driscoll SG, Bhan AK. Implantation site in normal pregnancy. Am J Pathol 1985; 118:76–84.
24. Starkey PM, Sargent IL, Redman CWG. Cell populations in human early pregnancy decidua: characterization and isolation of large granular lymphocytes by flow cytometry. Immunology 1988; 65:129–134.
25. Hunt JS, Manning LS, Mitchell D, Selanders JR, Wood GW. Localization and characterization of macrophages in murine uterus. J Leukocyte Biol 1985; 38:255–265.
26. Zheng Y, Zhou Z-Z, Lyttle CR, Teuscher C. Immunohistochemical characterization of the estrogen-stimulated leukocyte influx in the immature rat uterus. J Leukocyte Biol 1988; 44:27–32.
27. Bartocci A, Pollard JW, Stanley ER. Regulation of colony-stimulating factor 1 during pregnancy. J Exp Med 1986; 164:956–961.
28. Wang JM, Griffin JD, Rambaldi A, Chen ZG, Mantovani A. Induction of monocyte migration by recombinant macrophage colony-stimulating factor. J Immunol 1988; 141:575–579.
29. Tamada H, McMaster MT, Flanders KC, Andrews GK, Dey SK. Cell type-specific expression of TGF-β1 in the mouse uterus during the periimplantation period. Mol Endocrinol 1990; 4:965–972.
30. Wahl SM, Hunt DA, Wong HL, Dougherty S, McCartney-Francis N, Wahl LM, Ellingsworth L, Schmidt JA, Hall G, Roberts AB, Sporn M. Transforming growth factor-β is a potent immunosuppressive agent that inhibits IL-1-dependent lymphocyte proliferation. J Immunol 1988; 140:3026–3032.
31. Robertson SA, Mayrhofer G, Seamark RF. Uterine epithelial cells synthesize granulocyte-macrophage colony-stimulating factor and interleukin-6 in pregnant and nonpregnant mice. Biol Reprod 1992; 46:1069–1079.
32. Wang JM, Colella S, Allavena P, Mantovani A. Chemotactic activity of human recombinant granulocyte-macrophage colony stimulating factor. Immunology 1987; 60:439–444.
33. Ming WJ, Bersani L, Mantovani A. Tumor necrosis factor-alpha is chemotactic for monocytes and polymorphonuclear leukocytes. J Immunol 1987; 138:1469–1474.
34. Yoshida H, Hayashi S-I, Kunisada T, Ogawa M, Nishikawa S, Okamura H, Sudo T, Schultz LD, Nishikawa S. The murine mutation osteopetrosis is in the coding region of the macrophage colony stimulating factor gene. Nature 1990; 345:442–444.
35. Stewart CL, Kaspar P, Brunet LJ, Bhatt H, Gadi I, Kontgen F, Abbondanzo SJ. Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. Nature 1992; 359:76–79.
36. Shull MM, Ormsby I, Kier AB, Pawlowski S, Diebold RJ, Yin M, Allen R, Sidman C, Proetzel G, Calvin D, Annunziata N, Doetschman T. Targeted disruption of the mouse transforming growth factor-β1 gene results in multifocal inflammatory disease. Nature 1992; 359:693–699.
37. Kiso Y, Pollard JW, Croy BA. A study of granulated metrial gland cell differentiation in pregnant, macrophage-deficient, osteopetrotic (*op/op*) mice. Experientia 1992; 48:973–975.
38. Yelavarthi KK, Chen H-L, Yang Y, Fishback JL, Cowley BD Jr, Hunt JS. Tumor necrosis factor-alpha mRNA and protein in rat uterine and placental cells. J Immunol 1991; 146:3840–3848.
39. Peel S. Granulated metrial gland cells. Adv Anat Embryol Cell Biol 1989; 115:1–112.
40. Haynes MK, Shepley KS, Jackson LG, Tuan RS, Smith JB. Cytokine production in first trimester chorionic villi: detection of mRNAs and protein products in situ. Cell Immunol 1993; (in press).
41. LeFevre F, Martinat-Botte F, Guillomot M, Zouari K, Charley B, La Bonnardiere C. Interferon-γ gene and protein are spontaneously expressed by the porcine trophectoderm early in gestation. Eur J Immunol 1990; 20:2485–2490.
42. Parr EL, Parr MB, Zheng LM, Young JD-E. Mouse granulated metrial gland cells originate by local activation of uterine natural killer lymphocytes. Biol Reprod 1991; 44:834–841.
43. Bulmer JN. Decidual cellular responses. Curr Opin Immunol 1989; 1:1141–1147.
44. Hunt JS. Prostaglandins, immunoregulation, and macrophage function. In: Coulam C, Faulk WP, McIntyre JA (eds.), Immunological Obstetrics. New York: Norton Publ. Co.; 1992: 73–84.
45. Tawfik OW, Hunt JS, Wood GW. Implication of prostaglandin E2 in soluble factor-mediated immune suppression by murine decidual cells. Am J Reprod Immunol Microbiol 1986; 12:111–117.
46. Matthews CJ, Searle RF. The role of prostaglandins in the immunosuppressive effects of supernatants from adherent cells of murine decidual tissue. J Reprod Immunol 1987; 12:109–124.
47. Chen H-L, Yelavarthi KK, Hu X-L, Hunt JS. Analysis of transforming growth factor-β1 mRNA in virgin and pregnant rats by in situ hybridization. J Reprod Immunol 1994; (in press).
48. Clark DA, Falbo M, Rowley RB, Banwatt D, Stedronska-Clark J. Active suppression of host-vs-graft reaction in pregnant mice. IX. Soluble suppressor activity obtained from allopregnant mouse decidua that blocks the cytolytic effector response to IL-2 is related to transforming growth factor-β. J Immunol 1988; 141:3833–3840.
49. Redline RW, Lu CY. Specific defects in the anti-listerial immune response in discrete regions of the murine uterus and placenta account for susceptibility to infection. J Immunol 1988; 140:3947–3955.
50. Stewart I, Mukhtar DDY. The killing of mouse trophoblast cells by granulated metrial gland cells in vitro. Placenta 1988; 9:417–426.

51. Hunt JS, Soares MJ, Lei M-G, Smith RN, Wheaton D, Atherton R, Morrison DC. Products of lipopolysaccharide-activated macrophages (tumor necrosis factor-α, transforming growth factor-β) but not lipopolysaccharide modify DNA synthesis by rat trophoblast cells exhibiting the 80 kDa lipopolysaccharide-binding protein. J Immunol 1989; 143:1606–1613.
52. Hunt JS, Chen H-L, Hu X-L, Pollard JW. Normal distribution of tumor necrosis factor-α messenger ribonucleic acid and protein in virgin and pregnant osteopetrotic (*op/op*) mice. Biol Reprod 1993; 49:441–452.
53. Chen H-L, Yang Y, Hu X-L, Yelavarthi KK, Fishback JL, Hunt JS. Tumor necrosis factor-alpha mRNA and protein are present in human placental and uterine cells at early and late stages of gestation. Am J Pathol 1991; 139:327–335.
54. Hu X-L, Yang Y, Hunt JS. Differential distribution of interleukin-1α and interleukin-1β proteins in human placenta. J Reprod Immunol 1992; 22:257–268.
55. Nathan CF. Secretory products of macrophages. J Clin Invest 1987; 79:319–326.
56. Pollard JW. Regulation of polypeptide growth factor synthesis and growth factor-related gene expression in the rat and mouse uterus before and after implantation. J Reprod Fertil 1990; 88:721–731.
57. Robertson SA, Seamark RF. Granulocyte-macrophage colony stimulating factor (GM-CSF): one of a family of epithelial cell-derived cytokines in the preimplantation uterus. Reprod Fertil Dev 1992; 4:435.
58. McGregor JA, French JI, Lawellin D, Todd JK. Preterm birth and infection: pathogenic possibilities. Am J Reprod Immunol Microbiol 1988; 16:123–132.
59. Romero R, Emamian M, Wan M, Quintero R, Hobbins JC, Mitchell M. Prostaglandin concentrations in amniotic fluid of women with intra-amniotic infections and preterm labor. Am J Obstet Gynecol 1987; 157:1461–1467.
60. Romero R, Brody DT, Oyarzun E, Mazor M, Wu YK, Hobbins JC, Durum SK. Infection and labor. III. Interleukin-1: a signal for the onset of parturition. Am J Obstet Gynecol 1989; 160:1117–1123.
61. Romero R, Avila C, Santhanam U, Sehgal PB. Amniotic fluid and interleukin-6 in pre-term labor: association with infection. J Clin Invest 1990; 85:1392–1400.
62. Romero R, Manogue KH, Mitchell MD, Wu YK, Oyarzun E, Hobbins JC, Cerami A. Infection and labor. IV. Cachectin-tumor necrosis factor in the amniotic fluid of women with intraamniotic infection and preterm labor. Am J Obstet Gynecol 1989; 161:336–341.