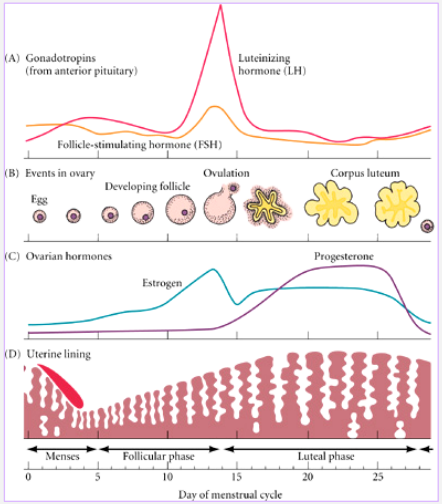
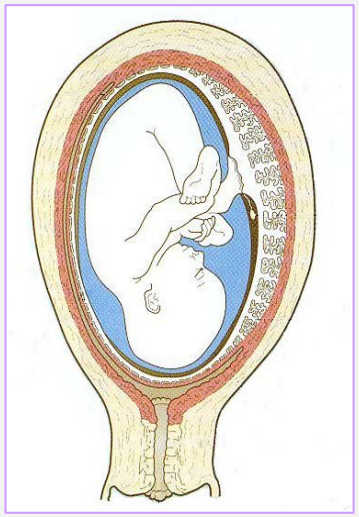
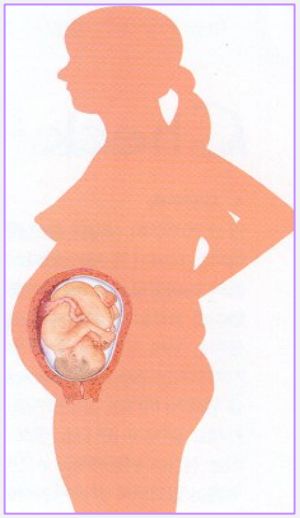
Action of Progesterone on Immune Cells







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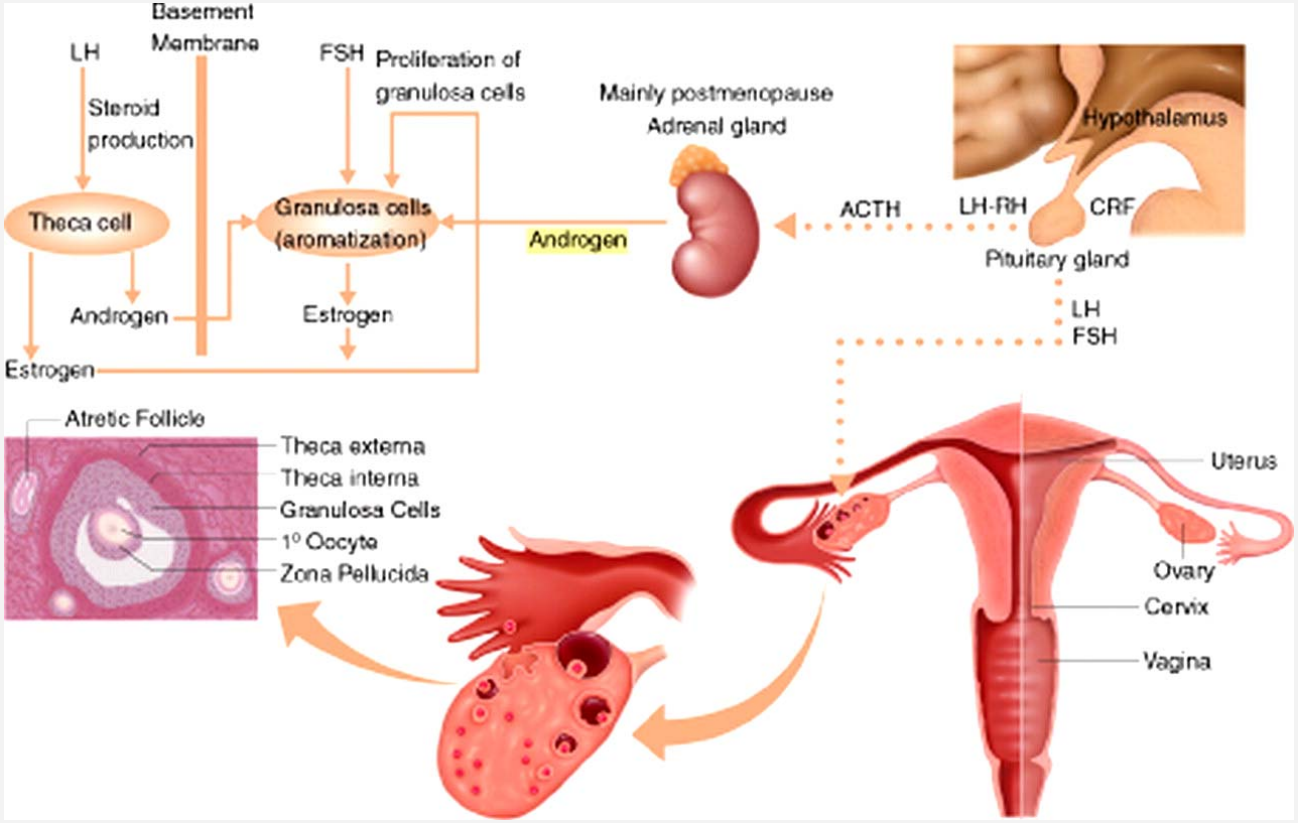
Introduction

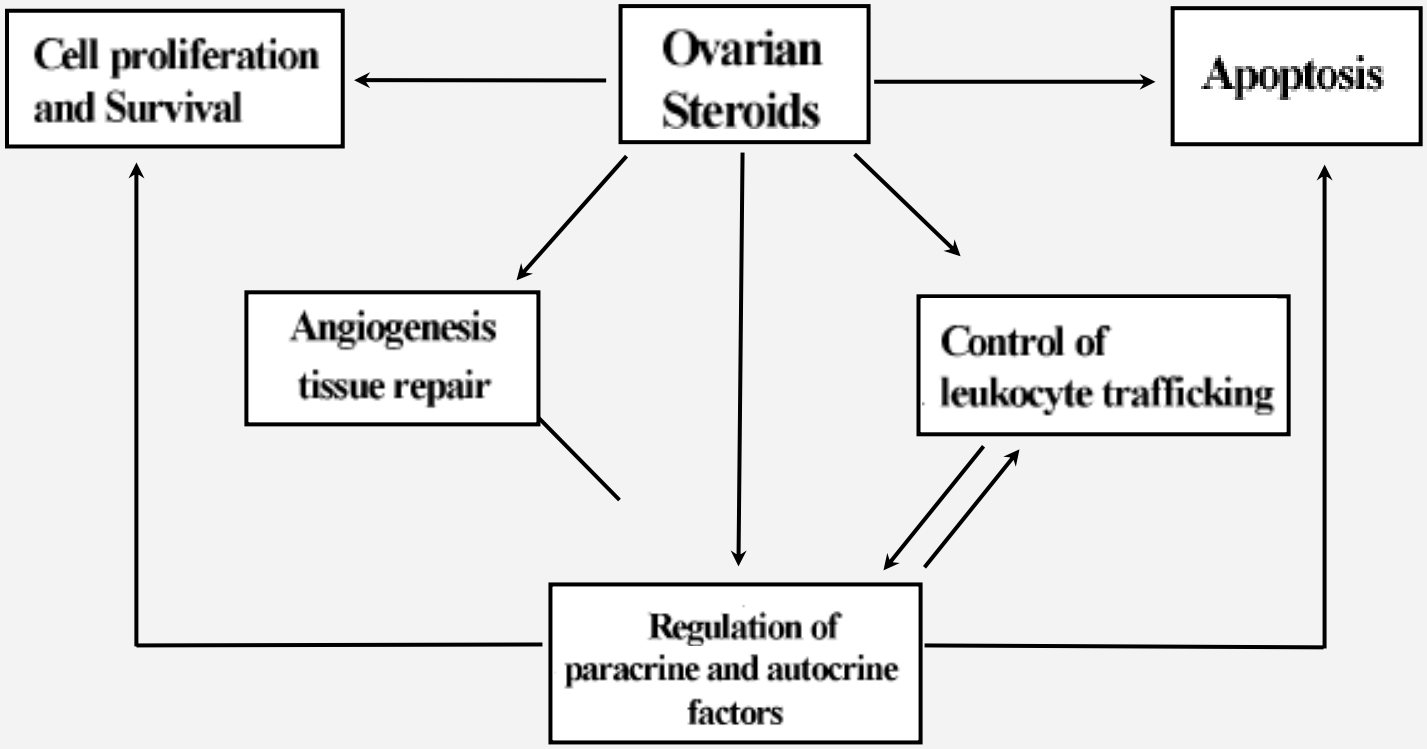
Synthesis of sex steroids

Estrogen

Progesterone



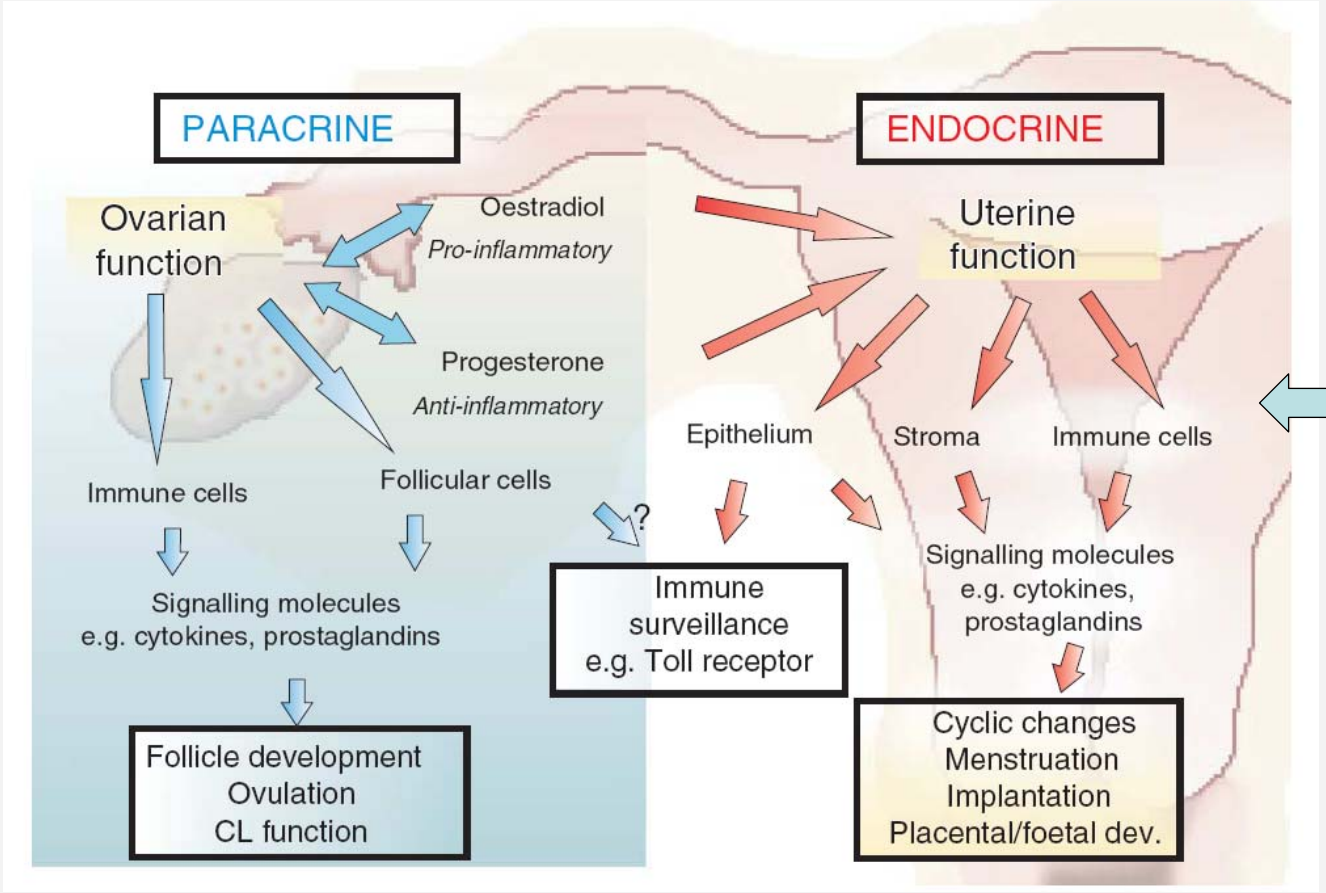
Regulation of endometrial events by ovarian steroids.

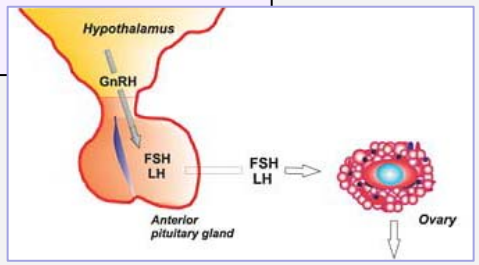


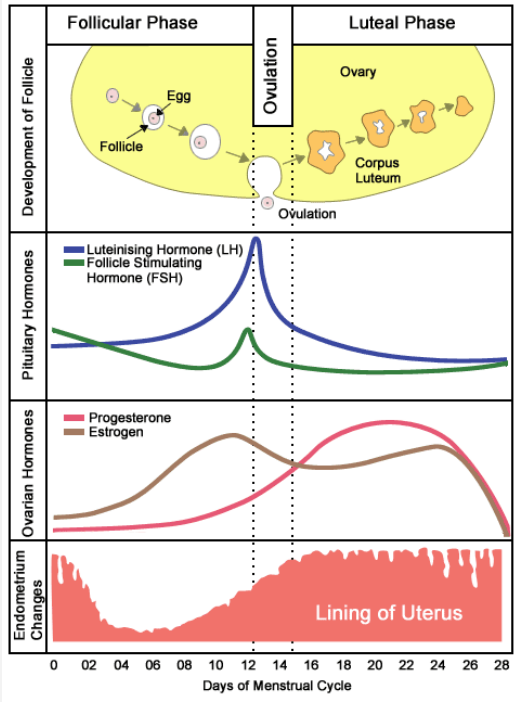
2-7 : Endocrine-immune interactions in human endometrium. Ann N Y Acad Sci 2004; 1034:50–63.

Introduction

Modulation of immune activity in the non-pregnant reproductive tract

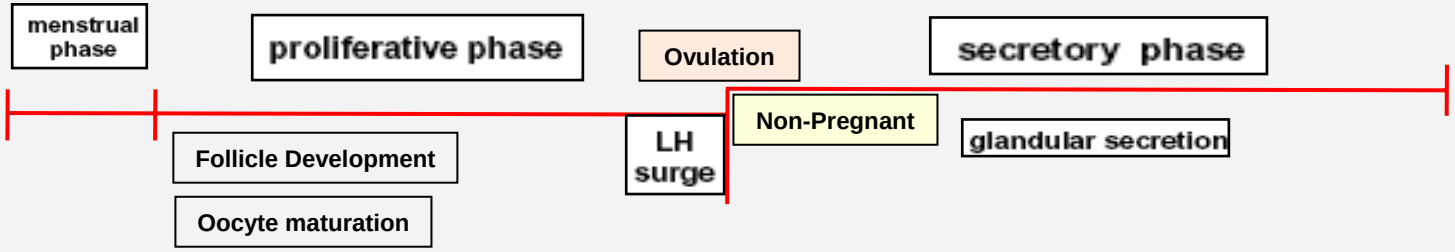






1: Reproduction. 2007 Sep;134(3):389-404.
Immunoendocrine aspects of endometrial function and implantation.

Female Reproductive Processes



Ovary

inflammatory-like mechanisms

inflammatory features of ovulation :

extracellular matrix degradation,
vascular changes,
expression of chemokines,
cell adhesion molecules, integrins
ultimate recruitment of leukocytes from the circulation

murine cumulus and granulosa cells :

express a range of innate immune-related genes important for cell survival and surveillance during ovulation.
(toll-like receptors : TLRs and scavenger receptors) exhibit phagocytic activity against bacterial particles.

……appear to exhibit immune surveillance activity

Follicular cells

anti-inflammatory mechanisms

mediated in part by glucocorticoids of adrenal origin that act through the receptor (NR3C1: nuclear receptor subfamily 3, group C, member 1) expressed on ovarian surface epithelial cells ….anti-inflammatory cortisol

At around the time of luteolysis (non-pregnant) :

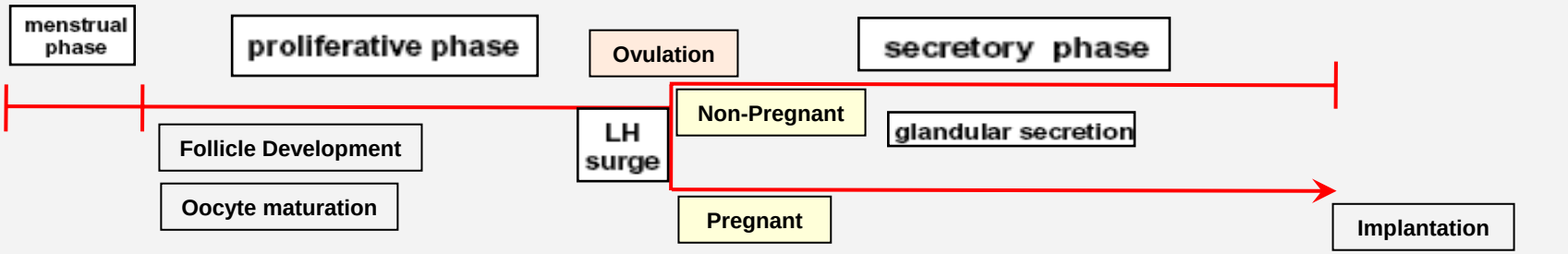
Neutrophils,
macrophages,
T-lymphocytes predominate in the corpus luteum (CL)

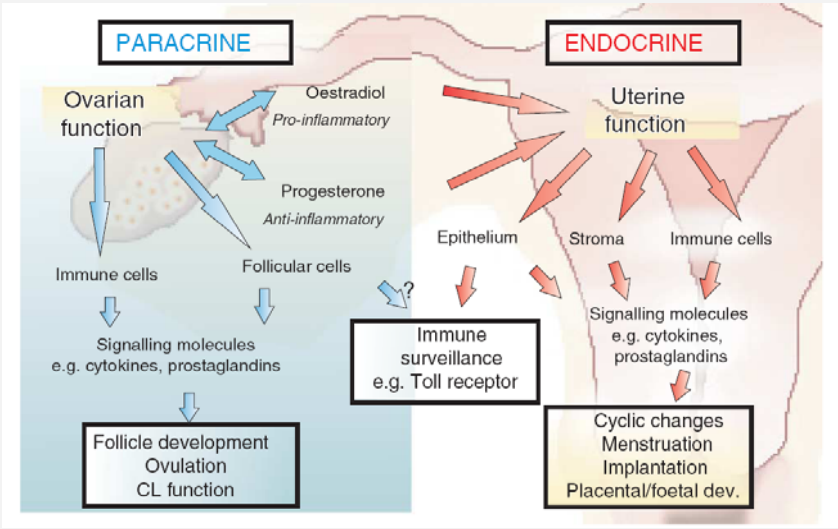
…destruction of the luteal cells (progesterone withdrawal)
clearing the dead and dying luteal cells up
… preventing a deleterious immune response to the surrounding ovarian tissue

Immune cells

Immunoendocrine crosstalk in reproductive biology

Endocrine- Immune Interaction in the Female Reproductive System





Uterine Endometrium

The uterus as a unique immune/mucosal organ

immune surveillance activity to:
commensal flora , infectious agents (bacteria, yeast, viruses)
sperm
semi-allogeneic blastocyst

Immune surveillance and response to pathogens in the non-pregnant reproductive tract

Endocrine- Immune Interaction in the Female Reproductive System

Uterine Endometrium

The uterus as a unique immune/mucosal organ

Epithelium

Express TLRs that recognise conserved pathogen-associated molecular patterns (PAMPs) present on micro-organisms.

Immune cells in stroma

Leukocytes

Leukocytes :10% (proliferative phase)
→ 20% (secretory phase)
→ 30% (early preg. Decidua).

Natural killer cell (NK) (70%) : TLRs

Macrophages (20%)

γδ T-cells

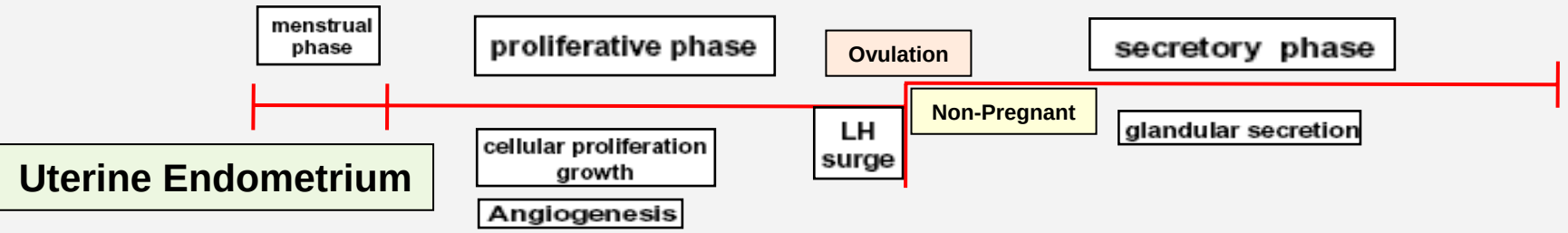
specialised T-cells,
polymorpho-nuclear leukocytes
B-cells

production of natural antimicrobial peptides, which also modulate host innate immunity.

- Defensins : antibacterial, antiviral and antifungal activity (neutrophils and epithelial sites)
- whey acidic protein (WAP) containing proteins :

protease inhibitors,
secretory leukocyte peptidase inhibitor (SLPI)
peptidase inhibitor 3 Express TLRs that recognise conserved pathogen - associated molecular patterns (PAMPs) present on micro-organisms.

Endocrine- Immune Interaction in the Female Reproductive System



inflammatory-like mechanisms

Estrogen

pro-inflammatory effects

influx of leukocytes into the uterus

increased levels of pro-inflammatory cytokines(esp, Il-1) from mast cells…asso. with the pre-implantation surge of oestrogen

anti-inflammatory mechanisms

Progesterone

prepare an oestrogen-primed endometrium for implantation
promotes uterine receptivity

block the influx of leukocytes

By 1. through progesterone receptor (PGR)
2. mediated through the NR3C1 (glucocorticoid receptor), which is expressed in the human endometrium across the menstrual cycle and in first trimester decidua (important component of tissue remodelling)

progesterone withdrawal
…triggers a series of immune-related events
…up-regulation of specific chemokines
…activated immune cells release matrix metalloproteinases

…endometrial breakdown (menstruation)

Pregnant — different set of local immune events ensures that pregnancy continues

The endocrine control of intrauterine inflammatory activity

Putative progesterone or progesterone receptor-sensitive endometrial immunoregulatroy genes

Gene name[a]	Symbol	Species	Target cell/tissue	Study	Progesterone effect	Reference
Chemokines and receptors						
Chemokine (C–C motif) ligand 2	*CCL2*	Human	Endometrium	*In vitro*	–	Critchley *et al.* (1999)
		Sheep	Endometrial eosinophils	*In vivo*	+	Asselin *et al.* (2001)
Chemokine (C–C motif) ligand 3	*CCL3*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Chemokine (C–C motif) ligand 8	*CCL8*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Chemokine (C–C motif) ligand 13	*CCL13*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Chemokine (C-X3-C motif) ligand 1	*CX3CL1*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Chemokine (C-X-C motif) ligand 1	*CXCL1*	Human	Endometrium	*In vivo*	+	**Catalano *et al.* (2007)**
Chemokine (C-X-C motif) ligand 5	*CXCL5*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Chemokine (C-X-C motif) ligand 12	*CXCL12*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Chemokine (C-X-C motif) ligand 13	*CXCL13*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Chemokine (C-X-C motif) receptor 4	*Cxcr4*	Mouse	Uterus	*In vivo*	–	Jeong *et al.* (2005)
Chemokine orphan receptor 1	*CMKOR1*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Chemokine-like factor superfamily 6	*CKLFSF6*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Interleukin-8	*IL-8*	Human	Endometrium	*In vitro*	–	**Critchley *et al.* (1999)**
Small chemokine (C–C motif) ligand 11	*Ccl11*	Mouse	Uterus	*In vivo*	–	Cheon *et al.* (2002)
Cytokines, growth factors and receptors						
Colony-stimulating factor 1	*CSF1*	Human	T-cells from decidua and peripheral blood	*In vitro*	+	**Piccinni (2006)**
Interleukin-4	*IL-4*	Human	T-cells from decidua and peripheral blood	*In vitro*	+	**Piccinni (2006)**
Interleukin-5	*IL-5*	Human	T-cells from decidua and peripheral blood	*In vitro*	+	**Piccinni (2006)**
Interleukin-15	*IL-15*	Human	First trimester decidual cells	*In vitro*	+	**Kitaya *et al.* (2000)**
Interleukin-1 receptor, type I	*IL1R1*	Human	Endometrial stromal cells	*In vitro*	+	Okada *et al.* (2003)
	Il1r1	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002)
Interleukin-4 receptor, α	*Il4ra*	Mouse	Uterus	*In vivo*	–	Cheon *et al.* (2002)
Interleukin-13 receptor, α2	*IL13RA2*	Human	Endometrial stromal cells	*In vitro*	–	Okada *et al.* (2003)
			Endometrium	*In vivo*	–	Catalano *et al.* (2007)
	Il13ra2	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002) and Jeong *et al.* (2005)
Leukaemia-inhibitory factor	*LIF*	Human	T-cells from decidua and peripheral blood	*In vitro*	+	**Piccinni (2006)**
Myeloid leukaemia factor 1	*MLF1*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Small inducible cytokine subfamily E, member 1 (endothelial monocyte activating)	*SCYE1*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Transforming growth factor, β1	*TGFB1*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Tumour necrosis factor receptor superfamily, member 1A	*TNFRSF1A*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Tumour necrosis factor receptor superfamily, member 21	*TNFRSF21*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)
Immune cell markers						
CD1d1 antigen	*Cd1d1*	Mouse	Uterus	*In vivo*	–	Jeong *et al.* (2005)
CD24a antigen	*CD24a*	Mouse	Uterus	*In vivo*	–	Cheon *et al.* (2002) and Jeong *et al.* (2005)
CD69 antigen (p60, early T-cell activation antigen)	*CD69*	Human	Endometrium	*In vivo*	–	Catalano *et al.* (2007)

CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen associated)	*Cd74*	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002)
Cytotoxic T-lymphocyte-associated protein 2α	*Ctla2a*	Mouse	Uterus	*In vivo*	+	Jeong *et al.* (2005)
Histocompatibility 2, class II antigen A, β1	*H2-Ab1*	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002)
Lymphocyte antigen 6 complex, locus A	*Ly6a*	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002)
Major histocompatibility complex, class II, DO β	*HLA-DOB*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Thymus cell antigen 1, θ	*Thy1*	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002)
Immune/inflammation modulators						
Complement component 3	*C3*	Mouse	Uterus	*In vivo*	−	Cheon *et al.* (2002) and Jeong *et al.* (2005)
Complement component 1, q subcomponent, β-polypeptide	*C1qb*	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002)
Galectin 15	*LGALS15; OVGAL11*	Sheep	Endometrial luminal and superficial glandular epithelium	*In vivo*	+	**Gray *et al.* (2005)** and Gray *et al.* (2006)
Histidine decarboxylase	*Hdc*	Mouse	Endometrium epithelial cells	*In vivo*	+	**Paria *et al.* (1998) and Jeong *et al.* (2005)**
Peptidoglycan recognition protein 1	*Pglyrp1*	Mouse	Uterus	*In vivo*	−	Cheon *et al.* (2002)
Progesterone-induced blocking factor 1[b]	*C13orf24*	Mouse, human, sheep	Systemic γ/δ T-cells (mouse and human), urine (human), endometrial cells (sheep)	*In vivo in vitro*	+	**Szekeres-Bartho *et al.* (1997a, 1999), Polgar *et al.* (2004), Lea *et al.* (2005) and Sandra *et al.* (2005)**
Secreted phosphoprotein 1	*Spp1*	Mouse	Uterus	*In vivo*	−	Cheon *et al.* (2002)
	SPP1	Sheep	Glandular epithelium	*In vivo in vitro*	−	**Johnson *et al.* (2000)**
Interferon-related proteins						
Interferon-induced transmembrane protein 3 (1–8U)	*IFITM3*	Sheep	Endometrium	*In vivo*	−	Gray *et al.* (2006)
Interferon, α-inducible protein 27	*IFI27*	Sheep	Endometrium	*In vivo*	−	Gray *et al.* (2006)
Interferon, α-inducible protein 6	*IFI6*	Sheep	Endometrium	*In vivo*	−	Gray *et al.* (2006)
Interferon-induced protein with tetratricopeptide repeats 1	*IFIT1*	Human	Endometrium	*In vivo*	−	Catalano *et al.* (2007)
		Sheep	Endometrium	*In vivo*	−	Gray *et al.* (2006)
Interferon-related developmental regulator 2	*IFRD2*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Interferon-stimulated gene, 20 KD	*Isg20*	Mouse	Uterus	*In vivo*	+	Jeong *et al.* (2005)
Intracellular signalling						
Immunoresponsive gene 1	*Irg1*	Mouse	Endometrium luminal epithelium	*In vivo*	+	Cheon *et al.* (2002), **Cheon *et al.* (2003), Chen *et al.* (2003)** and Jeong *et al.* (2005)
Janus kinase 1	*JAK1*	Human	Stroma, endometrial luminal and glandular epithelium	*In vitro*	+	**Catalano *et al.* (2003)**
Lymphocyte cytosolic protein 2	*LCP2*	Human	Endometrium	*In vivo*	+	Catalano *et al.* (2007)
Nuclear factor, IL-3, regulated	*Nfil3*	Mouse	Uterus	*In vivo*	+	Jeong *et al.* (2005)
Pre-B-cell leukaemia transcription factor 3	*PBX3*	Human	Endometrium	*In vivo*	−	Catalano *et al.* (2007)
Signal transducer and activator of transcription 1, 91 kDa	*STAT1*	Human	Endometrium	*In vivo*	−	Catalano *et al.* (2007)
Signal transducer and activator of transcription 5A	*STAT5a*	Sheep	Endometrium	*In vivo*	+	Gray *et al.* (2006)
	Stat5a	Mouse	Uterus	*In vivo*	−	Cheon *et al.* (2002)

(continued)

Table 1 *Continued.*

Gene name[a]	Symbol	Species	Target cell/tissue	Study	Progesterone effect	Reference
Suppressor of cytokine signalling 6	*SOCS6*	Human	Endometrium	*In vivo*	−	Catalano *et al.* (2007)
Prostaglandins and lipid metabolism						
Arachidonate 15-lipoxygenase	*Alox15*	Mouse	Uterus	*In vivo*	+	Cheon *et al.* (2002)
Prostaglandin-endoperoxide synthase 2	*PTGS2*	Human	Endometrium	*In vitro*	−	**Critchley *et al.* (1999)**
	PTGS2	Sheep	Endometrium luminal and glandular epithelium	*In vivo*	+	**Charpigny *et al.* (1997)** and Gray *et al.* (2006)
Proteinase inhibitors						
Serine (or cysteine) proteinase inhibitor, clade A (α-1 antiproteinase, antitrypsin), member 1	*SERPINA1*	Human	Endometrium	*In vivo*	−	Catalano *et al.* (2007)
Secretory leukocyte peptidase inhibitor	*SLPI*	Human	Endometrial glandular epithelial cells	*In vitro*	−	**King *et al.* (2000, 2003*c*)**
Uterine milk protein precursor A (family of SERine Proteinase INhibitors; SERPIN)	*UTMP*	Sheep	Uterine glandular epithelium	*In vivo*	+	**Ing *et al.* (1989)** and **Hansen (2007)**

[a]The names of the genes are presented according to the HUGO nomenclature (http://www.gene.ucl.ac.uk/nomenclature/). The term 'uterus' has been used when the whole tissue (myometrium and endometrium) has been subjected to gene analysis. Papers referring to microarray analyses are shown in roman. When the gene expression and regulation have been corroborated using a single gene approach, references are shown in bold. [b]Progesterone-induced blocking factor 1 (C13orf24) has been placed as an 'immune/inflammation modulator', since the structure of the protein is not classically recognised as a growth factor or a cytokine.

Putative progesterone or progesterone receptor-sensitive endometrial immunoregulatroy genes

use of transcriptomics：
large numbers of genes are screened simultaneously using broad range or targeted gene arrays

chemokines and their receptors
Interferons
cytokines and growth factors
Prostaglandins
Lipoxins
intracellular signalling molecules
immune modulators
specific immune cell populations
proteinase inhibitors

Putative progesterone or progesterone receptor-sensitive endometrial immunoregulatroy genes

Action of Progesterone on epithelial cells

chemokines and their receptors

selective expression of chemokines and chemokine receptors on trophoblast indicates that
the chemokine receptor network under the influence of progesterone might be critical for the process of implantation

Prostaglandins

prostaglandin production by the endometrium is important for implantation and early pregnancy

PTGS2, necessary for prostaglandin synthesis, is down-regulated by progesterone in human endometrium

Interferons

Putative progesterone or progesterone receptor-sensitive endometrial immunoregulatroy genes

Action of Progesterone on epithelial cells

cytokines and growth factors：

CSF1

progesterone induced expression of CSF1 by uterine epithelial cells

regulation of CSF1R-positive endometrial macrophages as one key endocrine–immune axis associated with implantation success

LIF

positively regulated by progesterone

Th2/anti-inflammatory paradigm associated with progesterone

Decidua and peripheral blood T-cells exposed to progesterone secrete IL-4 and IL-5
(progesterone induces a local Th2 bias *in utero*)

IL-13 receptor 2 (IL13Ra2) :
inhibited by progesterone
….promote anti-inflammatory activity important for endometrial function and/or implantation

IL-15 is also positively regulated by progesterone
……important in the stimulation of uNK cells in late secretory endometrium and first trimester decidua

down-regulation of TNF receptors

up-regulation of TGFB1

Putative progesterone or progesterone receptor-sensitive endometrial immunoregulatroy genes

Action of Progesterone on epithelial cells

Lipoxins

intracellular signalling molecules

Immune responsive gene 1

proteinase inhibitors

UTMP, uterine serpin
proteinase inhibitor (serpin superfamily of proteinase inhibitors)
exhibit weak antiproteinase activity
inhibit a wide range of lymphocyte functions
important in the inhibition of maternal immune responses directed against antigens expressed on the feto-placental unit
regulate cell proliferation possibly including trophoblast

Putative progesterone or progesterone receptor-sensitive endometrial immunoregulatroy genes

Action of Progesterone on epithelium & immune cells

immune modulators

LGALS15 (galectin 15)
important in the regulation of implantation and placentation

SPP1 (secreted phosphoprotein 1, osteopontin)
produced by uterine glandular epithelial cells and immune cells present in the endometrium and placenta.
epithelial cell-derived SPP1 is progesterone dependent
immune cell-derived SPP1 does not appear to be progesterone regulated
key link between progesterone and the activity of intrauterine immune cells

Histidine decarboxylase
progesterone-sensitive pro-inflammatory mediator

Progesterone-induced blocking factor (C13orf24)

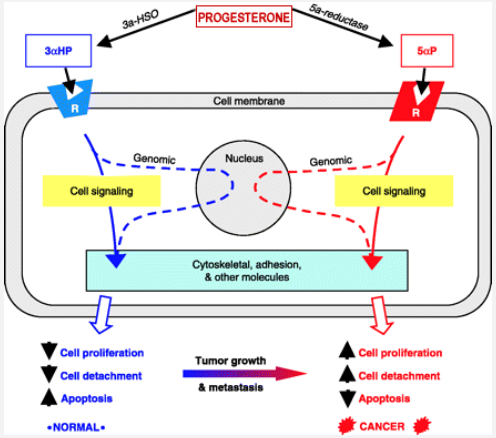
specific immune cell populations

Sex steroid receptors in the non-pregnant reproductive tract

progesterone receptor (PR)

PR positive cells:

Epithelial cell,
Activated T cell,
Macrophage



Genomic actions

nuclear receptor superfamily of the ligand-inducible transcription factors.
The binding of the ligand–receptor complex to the hormone response element in the DNA then triggers the transcription of oncogenes and genes encoding growth factors and cytokines.

Oestrogen, acting through the ESR1 receptor, differentially regulates the expression of the PGR.

2 isoforms of the PGR (PGRA and PGRB)

show cyclical variation in the glandular epithelium with a decline from the proliferative to the secretory phase
PGRB exhibited some variation in the stroma, as did both ESRs; however, the cell types were not identified.

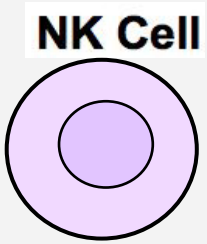
Non-genomic actions

membrane progesterone receptors :
non-genomic actions of progesterone
…do not influence gene expression
drive more rapid effects
such as activation of signalling cascades
and inhibition of transmembrane Ca^{2+} entry.
3 membrane progestin receptors(mPGR alpha, beta ß, gamma)
Endometrial mPGR alpha is up-regulated during the luteal phase and down-regulated in the myometrium with progesterone withdrawal

are present in ovary as well as the uterus
may also influence local immune mediators
implicated in T-cell immuno-suppression during pregnancy

"Progesterone metabolites such as 5alpha-dihydroprogesterone promote both mitogenic and metastatic activity in breast cells." *(Weibe J et al, J Steroid Biochem Molec Biol, 100(4-5), 2006)*

Action of Progesterone on uterine NK cells and T lymphocytes



- express ESR2 but not ESR1 or the progesterone receptors (oestrogen regulation)
- progesterone may indirectly affect NK cell activity through the induction of cytokines from neighbouring cells.
- also express the NR3C1, which is co-localised with HSD11B1 …suggests that cortisol may have an anti-inflammatory effect
- Another possibility : progesterone may act through NR3C1 (glucocorticoid receptor) or may affect NK cells via a non-receptor mechanism

Action of Progesterone on uterine NK cells and T lymphocytes

Anti-abortive effect of PIBF :

. inhibits arachidonic acid release by acting directly on the phopholipase A2 enzyme
. modifies the cytokine balance
. inhibits NK activity
. affect humoral immunity by increasing the production of asymmetric antibodies thought to have a blocking function

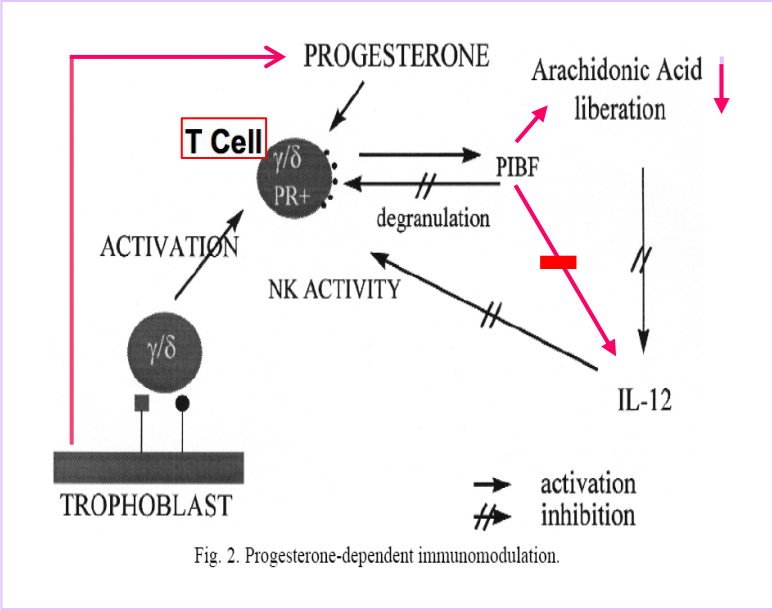
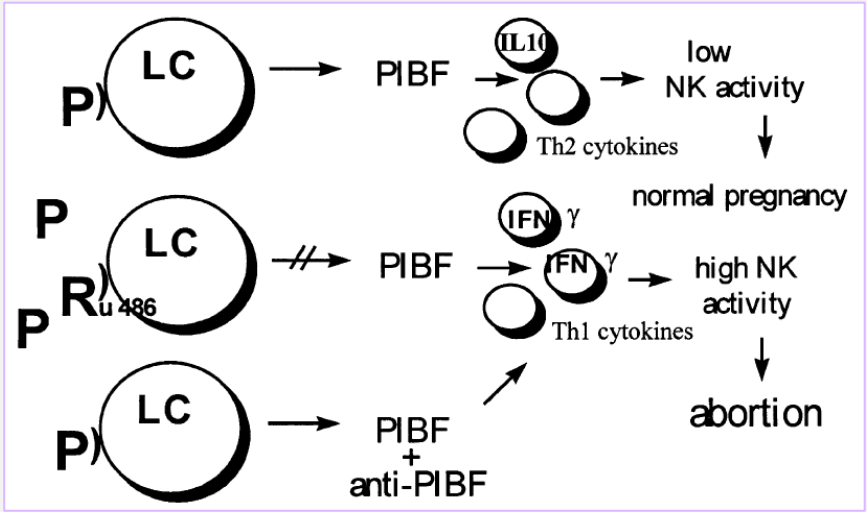
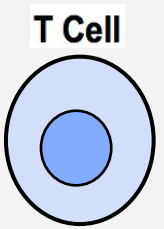


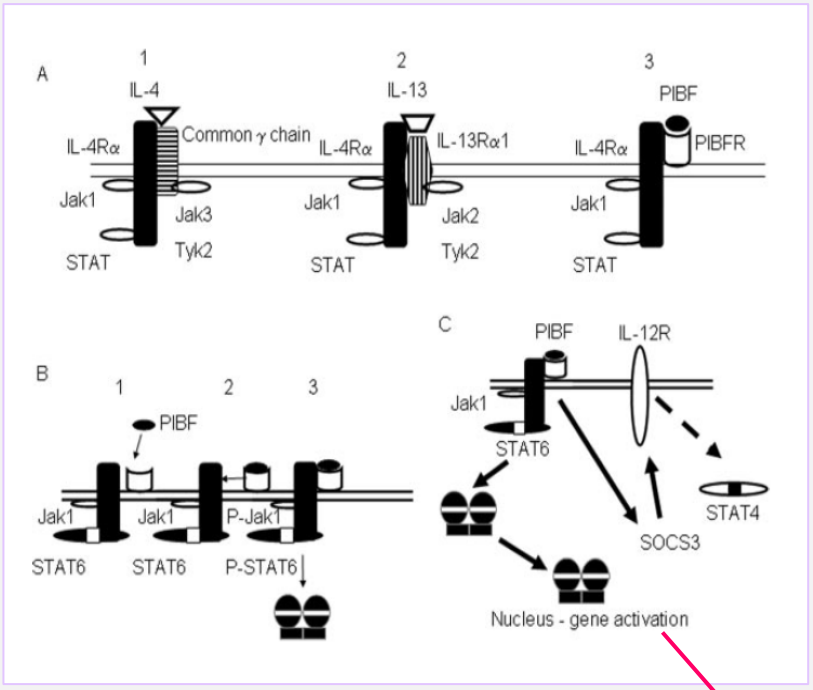
Fig. 2. Progesterone-dependent immunomodulation.

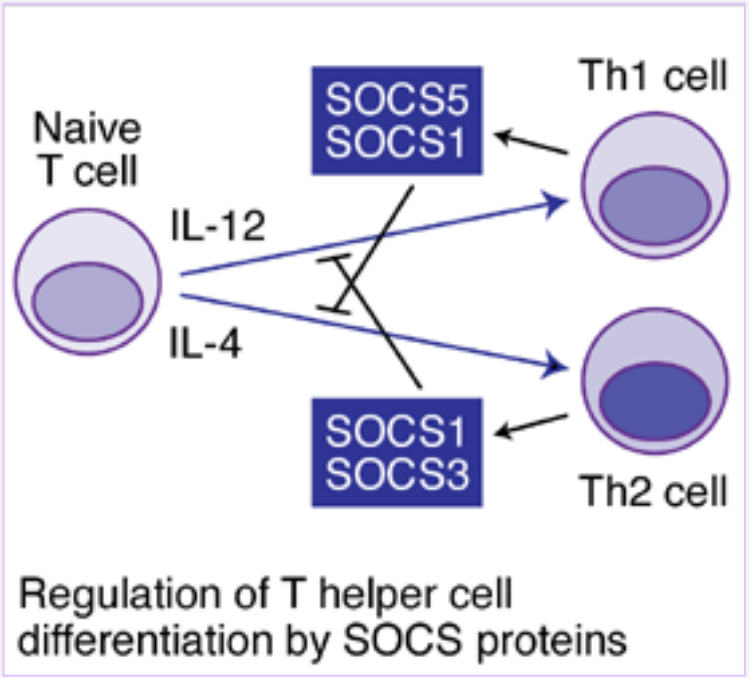


Action of Progesterone on uterine NK cells and T lymphocytes



Th2-biased immune response induced by PIBF





(3). *B*, Upon ligation, the PIBF receptor associates with IL-4Rα. *C*, PIBF binding to the PIBF receptor-IL-4Rα complex results in Jak1 phosphorylation, which in turn activates STAT6. STAT6 dimers move to the nucleus, where they activate a number of genes. PIBF-induced SOCS-3 binds to IL-12R and inhibits STAT4 phosphorylation.

Activation of Th2 responsive genes

Th2-biased immune response induced by PIBF

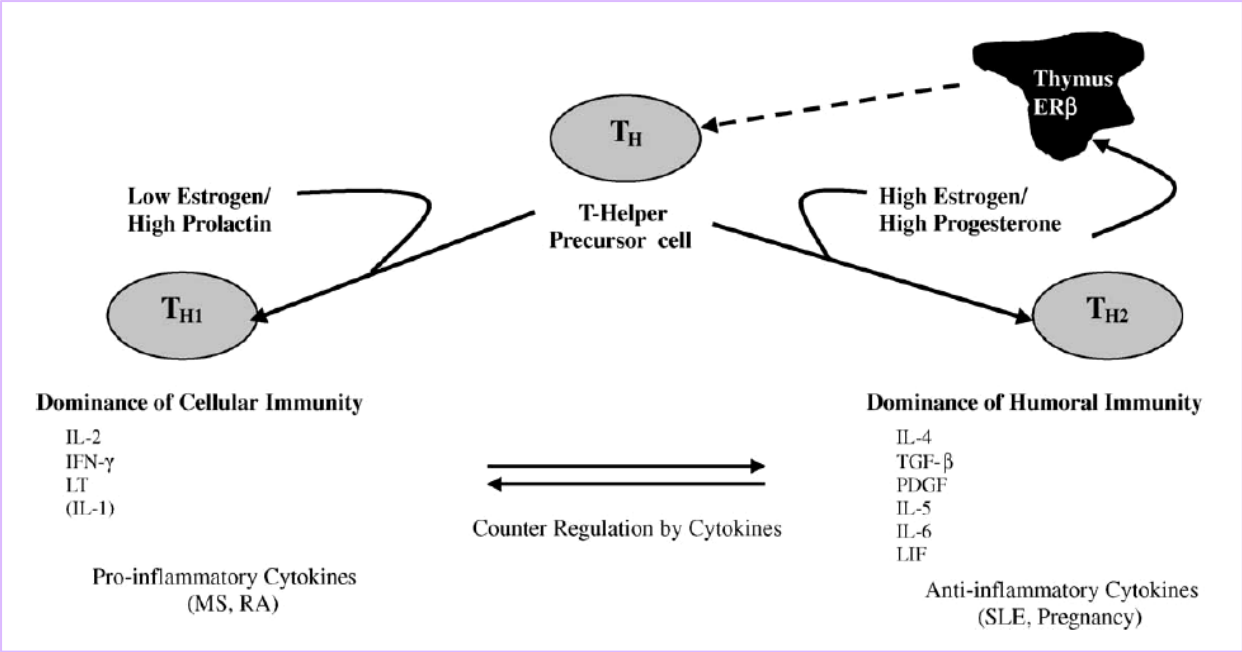


Fig. 1. The pathways of Th-1 and Th-2 lymphocytes. Adapted from Aschkenazzi et al. [5]. ER: oestrogen receptor; IL: interleukin; IFN: interferon; LT: lymphotoxin; MS: multiple sclerosis; RA: rheumatoid arthritis; TGF: transforming growth factor; PDGF: platelet derived growth factor; LIF: leukaemia inhibitory factor; SLE: systemic lupus erythematosus.

Progesterone and the immunology of pregnancy

Journal of Steroid Biochemistry & Molecular Biology 97 (2005) 389–396

Macrophage and reproduction

Macrophages play important roles in reproduction.

. involved in tissue remodelling and development of active immunotolerance to the conceptus.
. contribute to the regulation of steroidogenesis
. increased progesterone secretion by granulosa and luteal cells following co-culture with macrophages

Molecules driving mononuclear phagocyte differentiation in the female reproductive tract are principally regulated by sex steroid hormones and SP(seminal plasma)

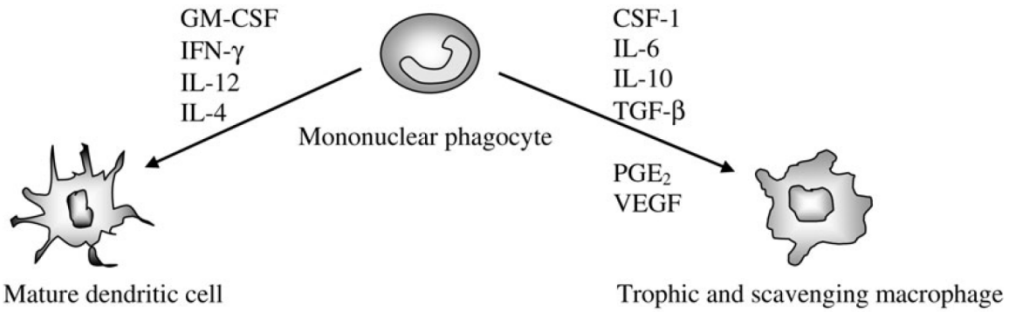
Progesterone and SP have marked immunosuppressive activity and
favour the maturation of trophic and scavenging macrophages

Inflammatory stimuli elicit the release of mononuclear phagocytes from bone marrow ……. favour the recruitment of macrophages in the reproductive tract.

Synthesis of CSF-1 is stimulated by estrogen and progesterone

GM-CSF is stimulated by estrogen and moderately inhibited by progesterone (Robertson *et al.*, 1996_).

Action of Progesterone on Macrophage



Estrogen
Stimulates production of GM-CSF and CSF-1 by uterine epithelial cells

Infections
Inflammation and immunogenic stimuli sustain differentiation of dendritic cells

Progesterone
Stimulates production of CSF-1 by uterine epithelial cells and of PGE_2 by macrophages suppresses production of GM-CSF by uterine epithelial cells

Seminal plasma
Contains high levels of TGF-β and PGE_2
Stimulates production of GM-CSF, IL-6 and IL-10 in the female reproductive tract

Non-immunogenic inflammation
Surgery, wounds, smoke sustain differentiation of trophic and scavenging macrophages

Differentiation of macrophages in the reproductive tract

Human Reproduction Vol.22, No.10 pp. 2577–2584, 2007
Advance Access publication on July 30, 2007

Action of Progesterone on Dendritic cells

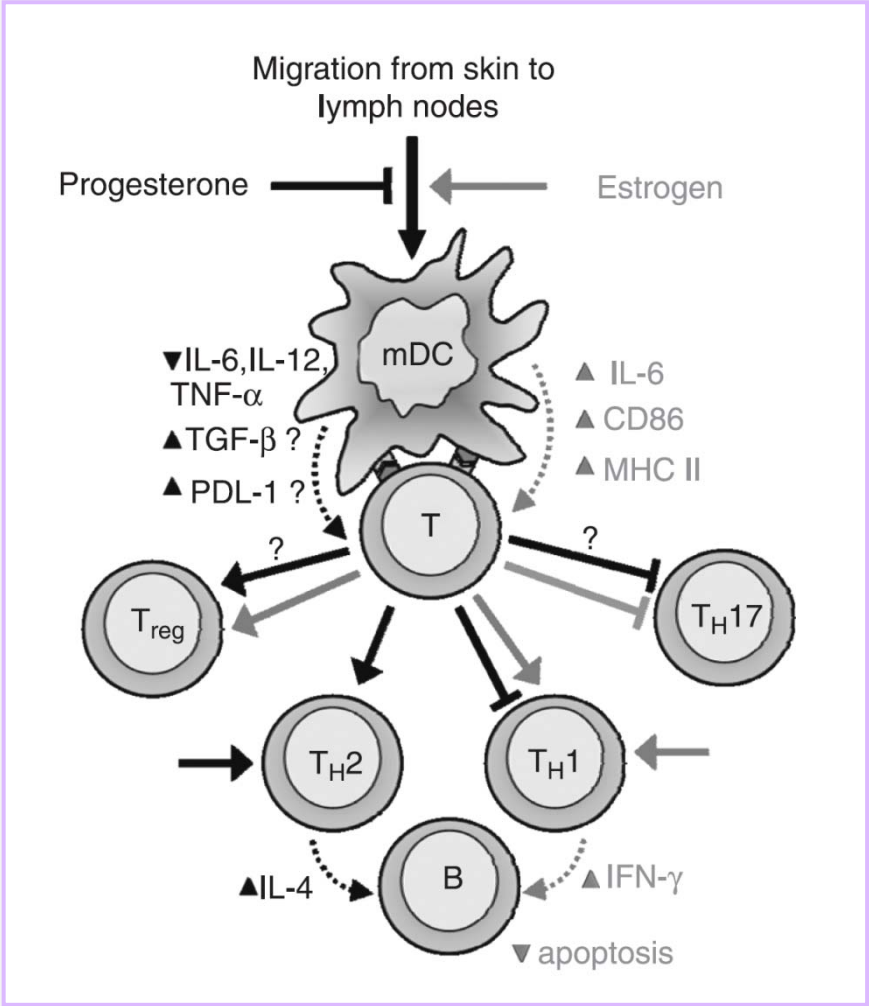


Figure 1. Progesterone and estrogen differentially regulate adaptive immune responses and autoimmunity through direct effects on DC functions.

Action of Progesterone on Dendritic cells

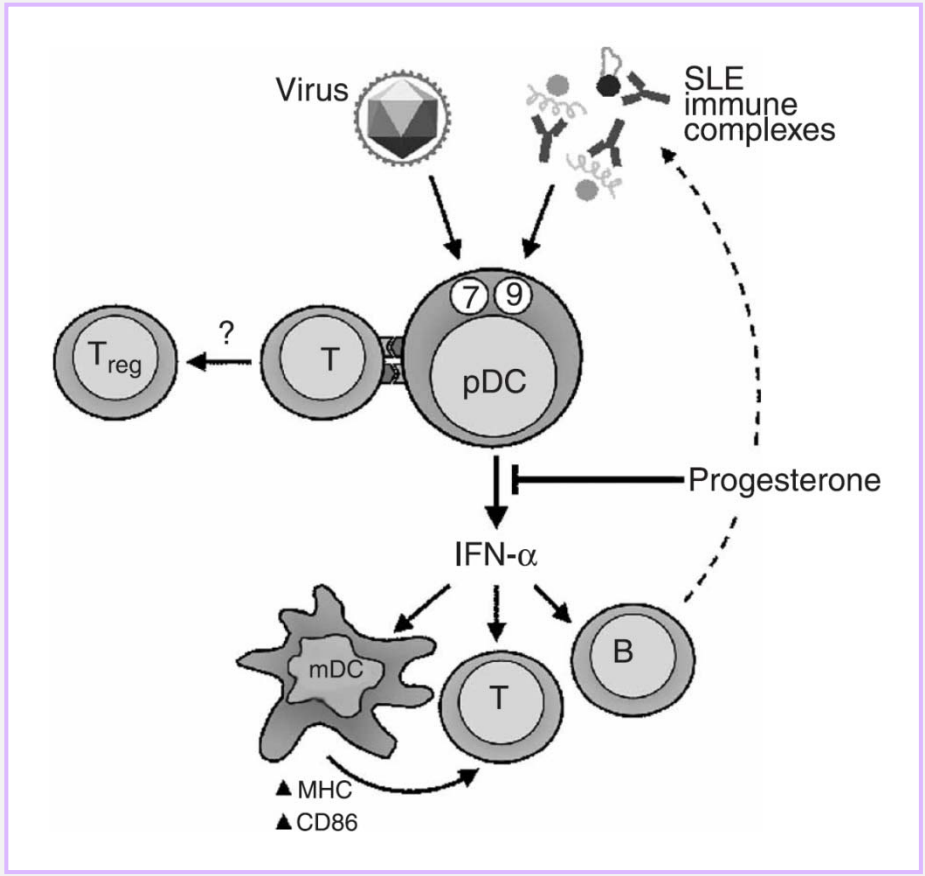


Figure 2. Progesterone regulates anti-viral immunity and autoimmunity through selective blockade of TLR7 and TLR9-mediated IFN-α production by pDCs.

Summary

Cyclical changes in the sex steroids :

influence a variety of genes in the ovary and uterus,
which act to protect these tissues against pathogens,
while simultaneously preparing them for ovulation,
menstruation or implantation. (immune-endocrine interaction)

During the period of increased uterine receptivity,

epithelial cells exhibit

increased toll receptor expression
altered produce specific antimicrobial peptides (e.g. SLPI)
….enhancing the ability to both detect and respond against PAMPs
on micro-organisms.

Sex steroids regulate the chemokines and receptors that act in the selective recruit of leukocytes.

progesterone have anti-inflammatory activities.

progesterone to influence NK cells(by PIBF) and macrophage

C13orf24 (PIBF) is produced systemically by PGR-positive T-cells
affects different aspects of immune function including reduced NK activity
induce production of anti-inflammatory Th2-like cytokines.

Crosstalk between the sex steroids and immune mediators (systemic and local) are central to all these functions

Key areas for future investigation

Rregulation and function of recently identified progesterone target genes

Manipulation of the sex steroid/glucocorticoid-regulated immunomodulatory pathways

For improved reproductive management in humans and animals.