Immunologia żeńskiego układu rozrodczego

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Protection of mucosal surface

Mechanical barriers and peristalsis
Desquamation of epithelial cells with attached microorganisms
Humoral factors: Mucin, acids, lysozyme, lactoferrin, peroxidase system antimicrobial proteins, interferon-α, complement Specific antibodies: IgA>>IgG>IgM
Cellular factors: Phagocytic cells, T cells, NK cells

Effector functions of secretory and serum IgA

	Secretory-IgA	Serum IgA
Molecular form	polymeric	monomeric
Subclass	IgA1 ≥ IgA2	IgA1 >>> IgA2
SC-mediated transport into secretions	Yes	No
J-chain expression	Yes	Mostly no
Origin of precursor cells	Bone marrow, no circulation	Peyer`s patches, IgA cells in circulation
Neutralization of antigens	Yes	Yes
Inhibition of bacterial adherence	Yes	?
Loss of bacterial plasmid	Yes	?
Inhibition from antigen uptake from mucosa	Yes	No
Enhancement of innate factors	Yes	Yes (?)
Suppression of inflammatory effects (phagocytosis, lysis, NK cell activity etc)	Yes	Yes

Cytokine help for the regulation of mucosal immunoglobulin response

Th subset	Cytokine production	Effect on IgA response
Th1	IL-2 IFN-γ Lymphotoxin β	Synergizes with IL-5/TGF-β → IgA synthesis Ig switch to IgG2a Development of Peyer`s patches
Th2	IL-4, IL-5 IL-6 IL-10	Differentiation to plasma cells IgA synthesis IgA synthesis
Th3	TGF-β	IgA isotype switching
T_R1	IL-10, TGF-β	Suppression of immune responses Downregulation of Th1

The lower genital tract in women

- The introitus, which is covered by a keratinized stratified squamous epithelium resembling skin
- The vaginal mucosa, which is covered by an aglandular non-keratinized stratified squamous epithelium
- The ectocervix, which is covered by a mucosal layer histological similar to that of the vagina
- The endocervix, which consists of a simple columnar epithelium with numerous glands

The upper genital tract in women

- consisting of:
  - the endometrium
  - the myometrium
  - the fallopian tube
  - the ovary
- These separate compartments have evolved to meet the different challenges and are precisely regulated by the endocrine system.

- Although the genital tract is considered to be a component of the mucosal immune system, it displays several distinct features not shared by other mucosal tissues or the systemic compartment. Differences include:
  - the endogenous flora,
  - the predominance of IgG,
  - the hormonal fluctuations that may modify mucosal immunity,
  - the need to be tolerant to sperm and to a developing fetus but also the ability to respond to sexually transmitted bacterial and viral pathogens.

Comparative features of humoral compartments of the human genital and intestinal tract

	Genital tract	Intestinal tract
Dominant Ig isotype	IgG ≥ IgA	IgA >>> IgG
Hormonal regulation	+++	-
Contribution of Ig from the circulation	++ (50%)	- (1%)
Inductive site for local and generalized humoral responses	- to +	++
Effector site	+	++
Expression of homing receptors on lymphocytes and ligands on ECs	LFA-1, ICAM-1, VCAM-1, α4β1	CCR9, CCR10, CCL25, CCL28, MAdCAM-1, α4β7, αEβ7
Response after intranasal immunization	++	+
Dominant function	Resident commensal flora in vagina vs exposure to sexually transmitted pathogens Acceptance of histoincompatible sperm/allogenic fetus	Induction of effective cell-mediated and antibody-mediated immune responses towards selected antigens Oral tolerance

- A major difference between the genital tract and the intestinal tract is that part of the genital mucosa is sterile, lacking the presence of a microbial flora.
- The female reproductive tract can thus be divided into two compartments
  - the vagina and ectocervix which host a commensal flora with predominantly lactobacilli which may play an important part in host defense
  - the endocervix, the uterus and fallopian tubes which are sterile.

- The mucosal immune system of the female genital tract is under strong hormonal control that regulates the transport of Igs, the levels of cytokines, the distribution of various cell populations, and antigen presentation in the genital tissues during the reproductive cycle.
- In addition to protecting against infectious agents, it must adapt to a spectrum of physiological events that includes fertilization, implantation, pregnancy, and parturition.
- A balance is maintained by sex hormones throughout the menstrual cycle to respond to the challenges of bacteria, yeast, and viruses without interfering with events that surround conception.

- Concentrations of cytokines and chemokines vary in the endometrium during physiological processes as well as pathological conditions.

- Many cytokines such as GM-CSF, TNF-α, TGF-β and LIF show temporal release patterns and are regulated by sex hormones.

- Four different patterns of cytokine expression related to the menstrual cycle were identified in CVL obtained from healthy ovulating women :
  - LIF, RANTES, and MIP-1α are detectable at menses only
  - IL-8, IL-6, TGF-β, and IL-1β are detected throughout the cycle but at highest levels at menses
  - M-CSF and epidermal growth factor (EGF) are found throughout the cycle but peak during the late proliferative phase
  - IFN-γ and TNF-α are detectable in a subpopulation of women during nonmenses stages of the cycle and may be associated with inflammatory events

- In the uterus, estradiol increases vascular permeability, which results in serum transudation of IgA and IgG into the uterine tissues.
- In contrast, movement of IgA and IgG in CVS is inhibited by estradiol and progesterone.
- Estrogen increases expression of pIgR and therefore IgA transport into the lumen when ECs were cultured with IL-4 and IFN-γ.
- IgG, however, moves down a concentration gradient from blood to uterine lumen under the influence of estrogen.

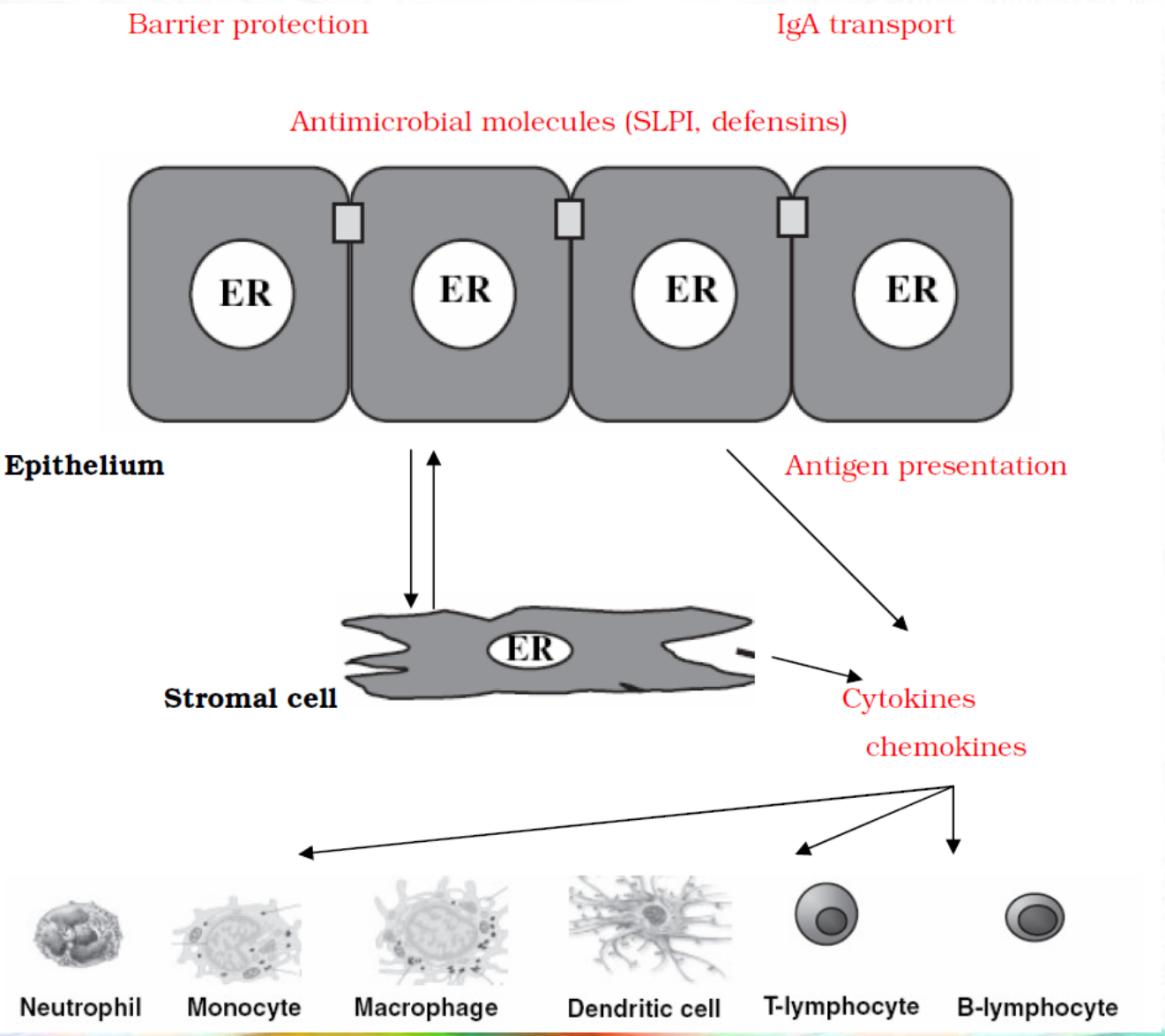
- It can be concluded that uterine ECs as well as APCs in the uterine stroma and vagina are capable of presenting antigen which initiates an immune response in the female reproductive tract.

- Moreover, sex hormones play a principal role in regulating antigen presentation in the genital tract.

Toll-like receptors and examples for their ligands

Receptor	Ligand	Origin of ligand
TLR1	Lipopeptides Soluble factors	Bacteria/mycobacteria *Neisseria meningitides*
TLR2	Lipopeptides Lipoteichoic acid Peptidoglycan Zymosan Lipoarabinomannan	Various pathogens Gram-positive bacteria Gram-positive bacteria Fungi Mycobacteria
TLR3	Double-stranded RNA	Viruses
TLR4	Lipopolysaccharide Taxol Fusion protein	Gram-negative bacteria Plants RS-Virus
TLR5	Flagellin	Bacteria
TLR6	Diacyl lipopeptides Lipoteichoic acid Zymosan	Mycoplasma Gram-positive bacteria Fungi
TLR7	Single-stranded RNA	Viruses
TLR8	Single-stranded RNA	Viruses
TLR9	CpG-containing DNA	Bacteria and viruses
TLR10	?	?
TLR11	?	Uropathogenic bacteria

Different immunoregulatory functions of ECs in the female reproductive tract



- Besides their role in the regulation of inflammation, macrophages have also been identified as important effector cells of ovarian function.
- The distribution of ovarian macrophages differs during the various stages of the menstrual cycle.
- The highest level of macrophages is in the vascular connective tissue and the theca-lutein areas of the corpus luteum during the periovulatory period.

- The specific localization and variations in distribution of macrophages in the ovary during different stages of the cycle as well as their presence in periovulatory human follicular fluid suggest that they play diverse roles in the folliculogenesis, tissue restructuring at ovulation and corpus luteum formation and regression.
- Ovarian macrophages secrete several cytokines such as TNF-α, IFN-γ, IL-1, IL-6, IL-10, IL-12 to regulate inflammation, as for example the state of ovulation.

Different functions of NK cells

Cytotoxicity
NK cells can kill virally infected cells and tumor target cells regardless of their MHC expression via their cytolytic granules containing perforin
Cytokine and chemokine secretion
Besides production of IFN-γ, NK cells also secrete TNF-α, GM-CSF, IL-5, IL-13, MIP-1 and RANTES. Killing and cytokine secretion seem to be mediated by different subsets of NK cells characterized by the intensity of expression of the CD56 marker on their surface
Contact-dependent cell costimulation
Serving as a bride between innate and adaptive immunity, NK cells express several costimulatory ligands including CD40L which allow them to provide a costimulatory signal to T cells or B cells

Neutrophiles in the ovary

- Also in the ovary neutrophils are present throughout the menstrual cycle.
- It has been show that low numbers of neutrophils infiltrate ovarian stroma but high numbers are present in the wall of the developing ovarian follicle.
- At ovulation, there was a marked increase in the density of these cells in the follicle wall, especially in the thecal layer, where they accumulate particularly around the point of imminent rupture.
- This suggests an active role for neutrophils in tissue remodelling during the ovulatory process.

Distribution of immunoglobulin-producing in different tissues of the female genital tract

Tissue	IgA	IgA1	IgA2	IgM	IgG
Fallopian tube	67	55	45	22	11
Endocervix	73	57	43	12	15
Ectocervix	79	59	41	10	11
Vagina	79	45	55	14	7

Distribution of IgA, IgG, S.C. and J chain in the tissues of the female reproductive tract

	IgA	J chain	SC/sIgA	IgG
Myometrium	—	—	—	—
Fallopian tube	+	+	+	+
Ovary	—	—	—	—
Endometrium	+/—	+/—	+	+
Endocervix	+++	+++	++	+/+++
Ectocervix	++	+	+/—	+
Vagina	+	+	+/—	++

Components of humoral and cellular immunity at different sites of the female reproductive tract

	Humoral immunity			Cellular immunity					
	Ig-producing cells	J chain	pIgR	T cells CD4 - CD8		NK cells	MA	DC	N
Myometrium	–	–	–	–	–	–	–	–	–
Fallopian tube	+	+	+	++	++	+	+	+	+++
Ovary	–	–	–	+	+	–	+/–	+/–	+
Endometrium	+/–	+/–	++	++	++	++	+	–	++
Endocervix	+++	++	+++	++	++	+	+	++	++
Ectocervix	++	+	+	+++	+++	+	+	++	++
Vagina	+	+	–	+++	+++	+	+	++	++

Immflamatory cells in the endometrium at three stages of the menstrual cycle

	Proliferative phase (days 10-12)	Secretory phase (days 22-23)	Menses (days 26-28)
Macrophages	+	++	+++ (6-15%)
Eosinophils	-	-	++ (3-5%)
Neutrophils	-	-	+++ (6-15%)
Mast cells	++	++	++ (3-5%)
T lymphocytes	+	+	+ (1-2%)
B lymphocytes	+/-	+/-	+
NK cells	-	+/++	+++ (5-6%)