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VAGINAL IMMUNITY – REVIEW ARTICLE

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INNATE IMMUNITY AND VAGINAL HEALTH

The innate immune system is the most primitive and evolutionary conserved arm of the immune system. It triggers a sequence of events leading to release of the pro-inflammatory cytokines and activation of the acquired immune system (T and B lymphocytes). Once T and B lymphocytes activated, these lymphocytes generate microbial antigen-specific cell-mediated and antibody-mediated immunity. A delicate balance is maintained by a complex interplay of local humoral, cell mediated and innate immunity in female reproductive system (Summers *et al.*, 2010). Innate immune system can recognize multiple microbes and components of their cell walls. The potential pathogens can be eliminated by multiple mechanisms, which include antimicrobial factors secreted by local epithelial cells, ingestion by resident phagocytes and activation of an inflammatory response (Janeway *et al.*, 2005).

1. Vaginal epithelial barrier: the first line of defense

The cervicovaginal epithelium and its tissue-associated phagocytes, macrophages and neutrophils, represent the first line of cellular microbial defense to provide a physical and chemical barrier. It act as sentinels and induces immune responses by the production of cytokines and chemokines (Wira *et al.*, 2005; Witkins *et al.*, 2007). Different defense mechanisms exhibited by cervicovaginal epithelium may be summarized as;

- **Mechanical**- tight junctions, air/fluid flow, ciliary rejection.
- **Chemical**- lysozyme, pH, defensins, surfactant opsonins.
- **Microbiological**- normal protective flora competition, antimicrobials like colicins.
- **Inductive**- receptors-mediated that recognize pathogens and signal other innate and adaptive immune responses.

Epithelial layer performs several other functions that aid in protection of vaginal health viz.

1) It provides a mechanical barrier to pathogen entry.
2) Activates both humoral and cell-mediated immunity.
3) It produces a variety of signals of cell injury such as chemokines, cytokines, prostaglandins and heat shock proteins for the attraction and activation of leukocytes.
4) It induces death of infected cells by necrosis, apoptosis, or phagocytosis.
5) It initiates and amplifies an acute inflammatory reaction.
6) It induces the release of protective cytotoxic substances (Nasu *et al.*, 2010).

Role of vaginal epithelium in innate immunity is well documented in literature. Epithelial cells recognize specific patterns in the arrangement of conserved key molecules on the surface called microbe-associated molecular patterns (MAMPs) or pathogen associated molecular patterns (PAMPs) which include lipo-polysaccharide (LPS), lipoproteins, peptidoglycans, lipo-arabinomannans and oligosaccharides (Yuan *et al.*, 2004). They are recognized by pattern recognition receptors (PRRs) which are widespread on a wide variety of immune cells, macrophages, neutrophils and dendritic cells that constitute a part of innate immunity (Janeway *et al.*, 2005). One family of PRRs called Toll-like receptors (TLRs) play an important role in innate immunity (Nasu *et al.*, 2010). Ligation of TLR by microbial products induces an inflammatory immune response which is characterized by the production of cytokines and antimicrobial factors and facilitates adaptive immune response (Medzhitov *et al.*, 1997). Recognition of a PAMP by an innate immune system component triggers a sequence of events leading to the release of pro-inflammatory cytokines and activation of the acquired immune system (T and B lymphocytes). Once activated, these lymphocytes generate microbial antigen-specific cell-mediated and antibody-mediated immune responses (Witkin *et al.*, 2007).

1.2 Role of Toll-like receptors (TLRs) in vaginal immunity

They are important components of vaginal innate immunity (Patton *et al.*, 2000). Ten TLRs have been identified so far, each with a distinct specificity in the lower genital tract of human females (Wira *et al.*, 2010). Each responds specifically to a distinct MAMP and are designed to recognize, with high specificity, various proteins, lipids, carbohydrates and nucleic acids of invading microorganisms and are typically located on either plasma membranes or intracellularly. This

recognition produces a rapid response by activating signaling cascades that trigger immune and inflammatory responses involving the production of pro-inflammatory mediators and activation of the acquired immune response (both humoral and cell-mediated).

The subcellular localization of different TLRs (**Figure 2.7**) correlates to some extent with the molecular patterns of their ligands. TLR1, TLR2 and TLR4 are located on the cell surface and are recruited to phagosomes after activation by their respective ligands (Blasius and Beutler, 2010). By contrast, TLR3, TLR7 and TLR9, all of which are involved in the recognition of nucleic-acid-like structures, are not expressed on the cell surface (Ahmad-Nejad *et al.,* 2002; Heil *et al.,* 2003; Matsumoto *et al.,* 2003). For example, TLR9 has recently been shown to be expressed in the endoplasmic reticulum and it is recruited to endosomal/lysosomal compartments after stimulation with CpG-containing DNA (Latz *et al.,* 2004).

TLR signaling is divided into two distinct signaling pathways, MyD88-dependent and TRIF-dependent pathway. Four adapter molecules, MyD88-Myeloid differentiation primary-response protein 88, Tirap-toll-interleukin 1 receptor (TIR) domain containing adaptor protein, Trif-TIR-domain-containing adapter-inducing interferon-β (TRIF) and Tram-TRIF and ash related adaptor molecule (TRAM) are known to be involved in TLR mediated cell signaling.

Mostly, the stimulation of TLRs triggers the association of MyD88 with TLRs (Burns *et al.,* 1998). MyD88-dependent response occurs on dimerization of TLRs either homodimers or heterodimers, and is utilized by every TLR except TLR3. MyD88 activates TRAF6, which in turn causing its degradation and allowing NFκB to diffuse into the cell nucleus and activate transcription and consequent induction of inflammatory cytokines. TLR3 and TLR4 utilize the TRIF-dependent pathway. dsRNA of viruses lead to the activation of TLR3 receptor, recruiting the adaptor TRIF. TRIF activates kinases which creates a branch in the signaling pathway and phosphorylates IRF3 allowing its translocation into the nucleus and production of interferon type I. TLR signaling ultimately leads to the induction or suppression of genes that orchestrate the inflammatory response (Alexopoulou *et al.,* 2001 ; Pudney *et al.,* 2005). TLR4 depends on other co-receptors such as MD-2 and CD14 for full ligand sensitivity for its recognition of LPS of pathogenic bacteria. LPS-Binding Protein (LBP) are known to facilitate the presentation of LPS to MD-2 (Yamamoto *et al.,* 2002). Role of various TLR's in inflammatory responses is summarized in **table 1** and illustrated in **figure 1.**

Table I: Pathogen-associated molecular patterns recoginition and expression properties of various TLR's of the Lower Female Reproductive Tract.

Type	Target	Recognition site	Constitutive Expression	Reference
TLR1	Gram positive bacteria	LPS, PGN, flagellin	epithelial cells of fallopian tubes, endometrium endocervix, ectocervix, vagina, uterine NK cells, vascular endothelial cells, and smooth muscle cells in cervical stroma as well as uterus	Pudney *et al.,* 2005; Horne *et al.,* 2008; Nasu *et al.,* 2010
TLR2	Bacteria	LPS, PGN, flagellin	epithelial cells of fallopian tubes, endometrium, cervix, vagina, smooth muscle cells of cervix and vagina, endometrial stromal cells, uterine NK cells. Highest levels in fallopian tubes and cervix	Nasu *et al.,* 2010
TLR3	Virus	dsRNA	tissue samples from fallopian tubes, endometrium, cervix, and vagina. Other expression in epithelial cells of fallopian tubes, endometrium endocervix, ectocervix, and vagina. Also in stromal fibroblasts of vagina, endocervix and in uterine	Alexopoulou *et al.,* 2001; Pudney *et al.,* 2005

			NK cells	
TLR4	Gram negative bacteria, virus	LPS, heat shock protein 60,glycoinositol phospholipids of protozoa, viral envelope proteins	fallopian tubes, endometrium cervix, vagina, declines from fallopian tubes to *vagina*, although presence in epithelial cells debated, TLR-4 activates NK and other immune response	Nasu *et al.*, 2010
TLR5	Bacteria	flagellin	epithelial cells of fallopian tubes, endometrium,vagina, endocervix	Hayasi *et al.*, 2001; Nasu *et al.*, 2010
TLR6	Bacteria, fungi	LPS,PGN, flagellin	expression in epithelial cells of fallopian tubes, endometrium, endocervix, ectocervix, vagina, uterine NK cells and stroma fibroblasts in vagina	Horne *et al.*, 2008
TLR7	Bacteria,viruses	ss RNA	epithelial cells of fallopian tubes, endometrium,cervix, vagina, uterine NK cells and endometrial stroma	Diebold *et al.*, 2004
TLR8	Bacteria,viruses	ss RNA	epithelial cells of fallopian tubes, endometrium, cervix, vagina, and endometrial stroma	Diebold *et al.*, 2004
TLR9	Bacteria, viruses	unmethylated deoxycytidyl-phosphatedeoxyguanosine (cpG) DNA	epithelial cells of fallopian tubes, endometrium, cervix, vagina, and endometrial stroma . It is able to distinguish between DNA sequences containing the dinucleotide CpG. In humans, this DNA sequence is heavily methylated, while in bacteria CpG is unmethylated	Hemmi *et al.*, 2000
TLR10	unknown	do	do	

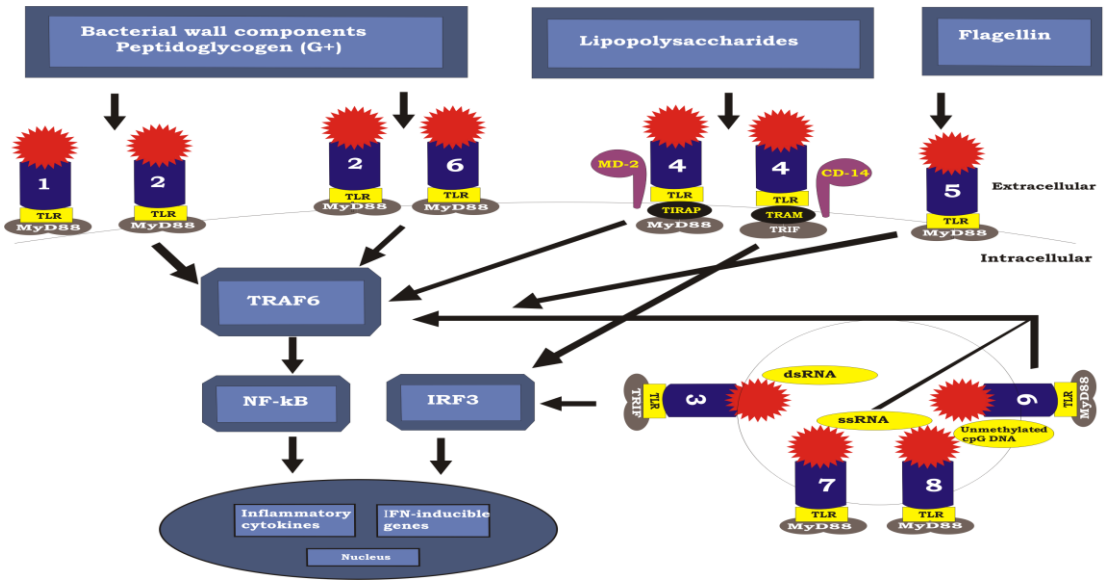

Fig. 1: PAMPs recognition by different TLRs and induction of immune responses.

1.2. Role of Adaptive immunity in vaginal health

The adaptive immune system, also known as the acquired immune system recognizes specific "non-self" antigens in the presence of "self" and generates the responses that are tailored to maximally eliminate specific pathogens or pathogen-infected cells. The adaptive immunity consists of antibody responses and cell-mediated responses, which are carried out by different lymphocyte cells, B cells and T cells, respectively. B cells are involved in the synthesis of antibodies that circulate in blood plasma and lymph, where they bind specifically to the foreign antigens. A key feature of the adaptive immune system is memory, the development of immunological memory, in which each pathogen is "remembered" by a signature antibody. In the lower genital tract, both B and T lymphocytes participate in recognizing specific components of individual microorganisms of the lower genital tract (Wira *et al.,* 2005).

1.3 Humoral immunity: The antibody responses are also called humoral immunity. Humoral immunity is so named because it involves substances found in the humours, or body fluids. Antibodies, also known as immunoglobulin, are large Y-shaped proteins, which are typically composed of two large heavy chains and two small light chains. B cells secrete antibodies that bind to microbial cells for preventing their entry into host cells, coat pathogens to induce phagocytosis and help in stimulation of immune responses through complement activation (Ravetch *et al.,* 2001). In mammals, there are five types of antibody: IgA, IgD, IgE, IgG, and IgM, differing in biological properties, each has evolved to handle different kinds of antigens. Humoral immunity in the human female genital tract has been well characterized (Kutteh *et al.,* 1999). IgG and IgA-secreting plasma cells are abundant in the lamina propria of the endocervix and scarce in the vagina, thus providing an evidence that immunological microenvironments exist in the lower female genital tract. Components are enlisted in (**Table 2**).

Table II: Components of humoral immunity in the lower female reproductive tract.

Components	Reference
Secretory IgA is produced by mucosal tissues of fallopian tubes ;	Nardelli *et al.,* 2003
Inhibits microbial adherence to surfaces, agglutinates resident microbes and reduces the hydrophobic nature of the microbes	Magnusson *et al.,* 1982
Stimulates antibody-assisted cell-mediated immunity and induces complement-independent antibacterial action of monocytes.	Lowell *et al.,*1980
Blocks microbial adhesions	Svanborg *et al.,* 1983
Neutralizes microbial toxins, enzymes and blocks their binding to target cells	Mansa *et al.,* 1986
Inhibits penetration of antigen into the mucosa, binds soluble antigens that facilitate their removal by mucus flow	Kilian *et al.,*1988
Augments T-cell antimicrobial activity	Tagliabue *et al.,*1988 or 84
Opsonization of microbes by mucosal phagocytes and coating of pathogens with IgA	Kilian *et al.,*1988
Antibody IgG is transudated from blood stream is locally produced and actively transported	Hocini *et al.,* 1995 Kozlowski *et al.,* 1997
Exhibits direct action against bacteria and viruses (immune exclusion of HIV particles)	Belec *et al.,* 1994
Binds and agglutinates bacteria and causes complement activation	Eriksson *et al.,* 1998

1.4 Cell-mediated immunity: Cell-mediated immunity does not involve antibodies but rather involves the activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. It consists of various subsets of T-lymphocytes which act in conjunction with other cytotoxic cells. Cell mediated immunity works by the direct action of cytotoxic or natural killer (NK) and antibody-dependent killer (K) cells. Cytotoxic T cells (CD8+) kill virus-infected cells; stimulatory cells (CD4+) activate other types of cells including macrophages and B cells (Wira *et al.,* 2005). **Table 3** summarizes role of various immune cells in female reproductive tract.

Table III: Components of Cell-Mediated Immunity in the female reproductive tract.

Cell type	Occurrence	Activity		Reference
		Innate immunity	Adaptive immunity	
Langerhans/ dendritic cells	Vaginal and cervical mucosa	Phagocytize bacteria or virus particles	Present antigen to T cells	Cole *et al.*, 2006
Neutrophils	Female genital tract (FGT)	Produces antipathogenic chemokines and cytokines	-	Wira *et al.*, 2005
T cells **• CD4+** **• CD8+**	Mucosal-associated lymphoreticular tissue within the lamina propria of cervix; CD8+ Most common epithelial T cells in FGT, cytotoxic CD4+	Direct cytotoxic action or stimulation of other immune responses	CD4+ activate macrophages, B cells. CD8+ kill virus-infected cells.	Pudney *et al.*, 2005 Cole *et a*l., 2006
NK cells (natural killer)	FGT	Kill virus-infected host cells	Kill virus-infected host cells	Vivier *et al.*, 2011
Macrophages	Mucosal-associated lymphoreticular tissue within lamina propria of cervix		Present antigen to T cell	Cole *et al*., 2006

2. Other components of vaginal defense system

2.1. Mucus: It is a protective barrier which blocks the spread of microbes from the vagina into the endometrial cavity and also concentrates a variety of pathogen fighting products (Tjabringa *et al.,* 2005). It is produced by apical epithelial cells and largely contains water and glycoproteins called mucins that hydrates the luminal surface and cover it with a mucus blanket (Cole *et al.,* 2006; Cone *et al.,* 2009). A component of the mucosal immune system is located in the female reproductive tract, and antibody producing B lymphocytes are present mainly in the vagina which locally produce both IgG and IgA class of antibodies (Mestecky *et al.,* 2000). Antibodies in turn recognize and bind to specific antigens on microorganisms, resulting in microbial killing by a complement-dependent mechanism.

2.2 Vaginal secretions: The vaginal fluid contains mucus as well as fluids from the endometrium, fallopian tubes and vestibular glands (Paavonen, 1983). Fluid secreted by vagina participates in mechanical defense of the mucosal surface as secretions continuously washes the pathogens towards vaginal opening. It also traps potential pathogens (Summers *et al.,* 2010). Lactic acid is a main component of vaginal fluid**,** but it also contains multiple aliphatic acids, alcohols and glycols, aromatic compounds, urea and proteins (Huggins *et al.,* 1976). The vaginal secretions also contain numerous antimicrobial substances such as defensins, cathelicidin, lactoferrin, lysozyme, calprotectin, elafin, secretory leukoprotease inhibitor (SLPI), and chemokines secreted by serous cells in submucosal glands. They all have a significant role in cervicovaginal immunity.

2.3 Defensins: These are small, positively charged peptides and are important component of innate immunity at the mucosal surface in the lower genital tract. These broad spectrum antimicrobials have efficacy against both Gram-negative and Gram-positive bacteria. They bind to the negatively charged bacterial surface to disrupt bacterial membranes resulting in cell lysis (Hancock *et al.,* 2001; Qualye, 2002). Human alpha-defensins, produced by neutrophils, are expressed by epithelial cells of the female genital tract (Ganz *et al*., 2003; Doss *et al.,* 2010). Human beta-defensins are produced by various epithelial cells of the female reproductive tract; some are induced by microbial components and some by pro-inflammatory cytokines (Horne *et al.,* 2008).

2.4 Secretory leukoprotease inhibitor (SLPI): SLPI is produced by macrophages and epithelial cells that inhibits proteolytic activity of neutrophil elastase, cathepsin G, trypsin and chymotrypsin and exhibits antimicrobial activity. SLPI is a potent inhibitor of enzymes that degrade proteins (Tjabringa *et al.,* 2005).

2.5 Mannose-binding lectin: This is an antimicrobial protein, present in the circulation as well as in vaginal secretions, recognizes carbohydrates patterns (N-

acetylglucosamine and fucose) on the surface of various pathogens and binds to microbes for inducing activation of complement system (Fraser *et al.,* 1998).

2.6 Elafin: This antagonistic factor is characterized by broad spectrum activity against bacteria and fungi (Stock *et al.,* 2009) expressed by epithelial cells. Elafin inhibits activity of neutrophil elastase and proteinase 3 (Tjabringa *et al.,* 2005).

2.7 Heat shock proteins: Antimicrobial heat shock proteins (such as hsp70) are present in the vagina that have been recognized recently. Its synthesis is greatly up-regulated in response to infection and inflammation. Intracellular hsp70 binds to other proteins for preventing their degradation and incorrect assembly. Extracellular hsp70 binds to TLR4 and promotes an immune response to the pathogens. hsp70 responds to abnormal flora by inducing release of nitric oxide in the vagina (Giraldo *et al.,* 1999; Genc *et al.,* 2006).

2.8 Nitric oxide: Nitric oxide has a potent antimicrobial activity against a wide range of pathogenic microorganisms (Bogdan *et al.,* 2001).

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