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Endocrine Control of Mucosal Immunity in the Female Reproductive Tract: Impact of Environmental Disruptors

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Abstract

The complexity of the human female reproductive tract (FRT) with its multiple levels of hormonally controlled immune protection has only begun to be understood. Dissecting the functions and roles of the immune system in the FRT is complicated by the differential hormonal regulation of its distinct anatomical structures that vary throughout the menstrual cycle. Although many fundamental mechanisms of steroid regulation of reproductive tract immune function have been determined, the effects of exogenous synthetic steroids or endocrine disruptors on immune function and disease susceptibility in the FRT have yet to be evaluated in detail. There is increasing evidence that environmental or synthetic molecules can alter normal immune function. This review provides an overview of the innate and adaptive immune systems, the current status of immune function in the FRT and the potential risks of environmental or pharmacological molecules that may perturb this system.

Keywords

Reproduction; Immunology; Toxicology; Environment; Fertility; Hormone

1. Introduction

Immune systems have been identified across the different kingdoms of life (Animalia, Plantae, Fungi, Protista, Archaea and Bacteria) that provide a formidable and sophisticated defense against pathogens (Marchalonis, et al. 1977; Rolff and Siva-Jothy 2003; Tiffin and Moeller 2006). Because of the implications in human health, however, many of the studies of the immune system have focused on the human. In order for the immune response to function properly, it must act rapidly with a response that is further self-limiting and causes no harm to the individual (Hickey, et al. 2011). The immune system must further retain a

"memory" for invading foreign organisms or pathogens in order to facilitate an even more rapid response to subsequent invasions.

1.1. Two Arms of the Immune System: Innate and Adaptive Immune Responses

1.1.1. The Innate Immune System—The innate immune system is evolutionarily ancient compared to the adaptive immune system with elements of it present across all the kingdoms of life. Its major components include: a) protective structural barriers (e.g. mucosal surface of the skin, gastrointestinal, reproductive and respiratory tracts); b) pattern recognition receptors such as Toll-like receptors (TLR), RIG-like receptors (RLR) and NOD-like receptors (NLR) that recognize conserved moieties also known as pathogen-associated molecular patterns (PAMPS) that are uniquely present in viral, bacterial and fungal pathogens; c) cytokines and chemokines that recruit immune cells (macrophages, dendritic cells, T cells) to the site of pathogen exposure; d) endogenous antimicrobials that actively inhibit pathogen survival; and e) innate immune cells (epithelial cells, stromal cells, macrophages, dendritic cells, neutrophils, natural killer cells) that drive this protective response and clear foreign pathogens.

1.1.2. The Adaptive Immune System—The adaptive immune system is composed of specialized cells, which are highly adaptable because of the ability for the acceleration of somatic mutations and irreversible genetic recombinations in the antigen receptor gene regions (Iwasaki 2010). The lymphocyte population can therefore express a vast number of distinct antigen receptors. Furthermore, as this gene rearrangement is irreversible in each cell, the progeny of each of these cells (e.g. memory B and T cells) will inherit the genes encoding the same antigen receptor specificity giving long-lasting specific immunity as well as mount stronger reactions when a pathogen is encountered again. The function of adaptive immune responses is to destroy invading pathogens and any toxic molecules they produce. Although the function of the adaptive immune system is to attack invading pathogens these responses can be destructive. It is therefore crucial that their immune responses are only in reaction to molecules that are foreign to the host and not to the host itself. The ability to distinguish *foreign*-molecules from *self-molecules* is a fundamental principal of adaptive immunity. A general comparison of the innate and adaptive immune system is given in Table 1. The innate and adaptive immune systems in the FRT have been described in detail in reviews (Wira and Fahey 2004; Wira, et al. 2005b; Wira, et al. 2011). The variety of immune responses to the plethora of pathogens that can infect the FRT maintains health for the woman and her potential/unborn child.

1.2. Mucosal vs. Systemic Immunity

For many years, the studies on the immune system emphasized "systemic" immune responses with much emphasis on circulating cells, antibodies and other soluble factors in body fluids. It has, however, become increasingly apparent that the body's mucosal surfaces, which separate the external from the internal environment, are a critical first line of immune defense. These physical barriers constantly confront environments, which are rich in potential pathogens, and thus they possess mechanisms to protect against invading hostile pathogens while harboring harmless molecules such as food, airborne antigens or commensal bacterial flora. To meet these specialized needs, mucosal surfaces has developed

as a complex but sophisticated immune system (innate and adaptive), which is both anatomically and functionally distinct from the systemic immune system (Heremans 1974; Mestecky and McGhee 1987). Characterized by the presence of secretory IgA and IgG, immune protection is also dependent upon T- and B-lymphocytes, monocytes and macrophages, as well as other antigen-presenting cells which recognize and respond to antigenic challenge (Brandtzaeg and Prydz 1984; McDermott and Bienenstock 1979; Ogra, et al. 1981; Underdown and Schiff 1986; Wira, et al. 2003). A summary of the general functions of some of the major proteins involved in mucosal immunity is given in Table 2. These immune factors contribute to immune responses in multiple ways, including acting as antimicrobials against bacterial, fungal and viral pathogens, attracting a diverse immune cell population, activating/differentiating immune cells, stimulating secretion of other cytokines and chemokines, affecting proliferation of immune cells and regulating proteolytic enzymes (Wira, et al. 2005a).

1.2.1 Sexually Transmitted Diseases—According to the World Health Organization (WHO), sexually transmitted diseases (STDs) are one of the most serious public health issues with 340 million new cases of potentially curable STDs (Syphilis, Gonorrhoeae, Chlamydia and Trichomoniasis) occurring annually amongst adults aged 15–49 years (WHO 2007). In developing countries STDs and their complications rank in the top five disease categories for which adults seek health care. Infection with STDs can lead to acute symptoms, chronic infection and serious delayed consequences such as infertility, ectopic pregnancy, cervical cancer and the untimely death of infants. Human Immunodeficiency Virus (HIV) has caused approximately 25 million deaths with an additional 33.4 million people infected world-wide (UNAIDS 2007). Women living with HIV make up approximately 60% of the infected patients (UNAIDS 2009). The majority of HIV and STD transmission events occur across the mucosal surface of the FRT. Thus defining and understanding the immune response at this site is essential in preventing the spread of these pathogens.

2. Immunology of the female reproductive tract

While most research has concentrated on the mucosal immunity of the gastro-intestinal or respiratory tracts, emerging studies on the function of the immune system in the FRT have demonstrated the critical role it has in balancing protection against STDs while allowing the survival of foreign sperm and an allogeneic embryo (Fahey, et al. 2011; Kutteh 2005; Wira, et al. 2010; Wira et al. 2005b; Wira et al. 2011). Studies by Wira and colleagues have shown that all aspects of the innate and adaptive immune systems throughout the female reproductive tract are under sex hormone control.

Each of the five anatomical sites of the FRT (Fallopian tubes, endometrium, endocervix, ectocervix and vagina), while functioning separately, provides a collaborative environment to both protect the host from infection while allowing fertilization of the egg and subsequent implantation of the embryo which expresses the sperm’s foreign genes. Each of these anatomical sites is differentially controlled by estradiol and progesterone, which in turn modulate the production and secretion of various immune factors at different times of the menstrual cycle. Extensive studies (Wira, et al. 2005a; Wira et al. 2010; Wira et al. 2005b;

Wira, et al. 2005c; Wira, et al. 2002) have defined how these functions are synchronized to optimize the chances for successful fertilization, implantation, and pregnancy.

2.1. Immune cells involved in immune function in the FRT

In order to begin to dissect the immune function of the distinct tissues of the FRT it is important to identify the immune cells, their location in these tissues as well as their potential regulation by steroids. Table 3 summarizes the immune cells that have been identified in the human FRT as well as their general functions and their expression of the sex hormone (estrogen and progesterone) receptors. Collectively these studies show that there is a full set of active immune cells in the FRT and that the differential regulation of these cells in the distinct compartments of the FRT is critical for reproductive success. Of further interest is that the FRT immune cells express steroid hormone receptors suggesting that they are directly responsive to hormonal stimuli thus demonstrating the complex interplay between endocrine, reproductive and immune function (Wira et al. 2005a).

2.2. Epithelial and Stromal Cells of the FRT and Their Roles in Immunity

In addition to the full set of immune cells distributed throughout the FRT, epithelial and stromal cells are capable of both mounting an immune response and modulating immune cell function (Wira et al. 2005c). A summary of these properties is given in Table 4. Collectively, these studies show which hormone-regulated reproductive tract cells contain hormone receptors as well as surface receptors involved in recognizing (e.g. TLR) and responding (cytokines, chemokines and endogenous microbicides) to pathogens (Schaefer, et al. 2005). Also shown in Table 4 is how secreted immune factors vary during the menstrual cycle (see column on secreted immune factors and Table footnote). It is evident that cells and their immune response potential, as well as their ability to be directly modulated by sex hormones, vary throughout the FRT.

2.3. Key Immunoregulatory Modulators of the Innate and Adaptive Immune System in the FRT

As summarized in Table 4, many peptide/protein molecules, including chemokines, cytokines, proteases, protease inhibitors, immunoglobulins, matrix metalloproteases, antimicrobials and growth factors have been identified in the FRT and could potentially modulate immune function (Fahey et al. 2011; Wira et al. 2010; Wira et al. 2011). It has been estimated that there are over 600 proteins in the fluids from cervical lavages (Shaw, et al. 2007). There are likely to be many immune factors that have not been identified. It is apparent that these observations address a critical field of women's health that requires further study. Of particular interest is a growing body of evidence that commensal bacteria in the lower female reproductive tract as well as at other mucosal surfaces are dependant on estrogen-driven presence of glycogen in epithelial cells and play a central role in providing immune protection (Boskey, et al. 2001). For example, the acidic microenvironment of the vagina is maintained by lactic acid producing commensal bacteria, the most common of which is *Lactobacillus* found in normal pre-menopausal healthy women (Witkin, et al. 2007). In addition to regulating vaginal pH, specific commensal microdomes protect against HIV infection (Ahmed, et al. 2010). *Escherichia coli*, *Veillonella parvula* and *Neisseria*

mucosa suppress HIV-1 infection through TLR-4 activation. In contrast, TLR-2 activation by *Lactobacillus acidophilus*, *Prevotella melaninogenica*, *Prevotella bivia* and *Mycobacterium smegmatis* enhanced infection (Ahmed et al. 2010). Further research is needed to more fully understand how commensal bacteria alter the vaginal immune protection.

2.3.1. Cytokines, Chemokines and Antimicrobials—Cytokines and chemokines are a structurally and functionally diverse group of proteins (Cannon 2000; Foster, et al. 2004a; Foster, et al. 2004b; Liles and Van Voorhis 1995; Steinke and Borish 2006). These proteins were initially shown to act as mediators and regulators of immune processes but studies have also shown that cytokines are also produced by cells other than immune cells and can also affect non-immune cells. The most common cytokines include: (a) lymphokines (secreted by activated lymphocytes, especially T helper cells); (b) interleukins (mediators between leukocytes); (c) chemokines (small cytokines primarily responsible for leukocyte attraction and migration); and (d) monokines (produced by mononuclear phagocytic cells). Cytokines are produced by cells of both the innate and adaptive immune systems and may act on many cell types (*i.e.*, they are **pleiotrophic**). In many instances they may have similar actions (*i.e.*, **redundancy**). Redundancy is due to the usage of the cytokine receptors, which are shared amongst multiple signaling molecules. For example the Type I interferon receptor complex in humans is shared amongst 13 isoforms of IFNα and one isoforms of IFNβ, IFNκ, IFNω and IFNε respectively all of which are believed to generate a protective antiviral response.

Cytokines can induce both damaging and protective responses as well as induce or suppress synthesis of other cytokines. These networks are made even more complex by the receptors that bind these regulatory molecules (Kitamura, et al. 1992; Lopez, et al. 2010; Miyajima, et al. 1992). The response of cytokine/chemokine binding to receptors is associated with various factors including the affinity of binding as well as differential expression and signal transduction pathways.

With respect to the FRT, it has been shown that cytokines and cytokine receptors are expressed by both immune and non-immune cells, and can be regulated by steroid hormones. Cytokines influence a range of uterine functions during the menstrual cycle, as well as implantation, pregnancy and labor Tribe (Orsi and Tribe 2008). There are intricate and dynamic synergistic interactions among individual cytokines, how they are modulated by pregnancy hormones and how perturbations to cytokine signaling can be associated with adverse pregnancy outcomes, such as miscarriage, pre-eclampsia, preterm labor and fetal brain injury.

2.3.2. Immunoglobulin Secretion in the FRT—It has long been known that immunoglobulins (both IgG and secretory IgA) are present in the genital tract of women and that the levels of these proteins vary throughout the reproductive tract and during the menstrual cycle (Kozlowski, et al. 2002; Lu, et al. 1999; Schumacher, et al. 1977; Usala, et al. 1989). While origin of these antibodies is uncertain, it is apparent that both plasma-derived and locally produced antibodies contribute to the immunoglobulin pool (Kutteh 2005). More recent studies have confirmed these early results. Women vaccinated with the

human papillomavirus (HPV) had cervical antibody titers that were highest in the proliferative phase but decreased approximately nine-fold around ovulation, and increased 3-fold during the luteal phase (Nardelli-Haefliger, et al. 2003). Whether decreases in antibody titer around ovulation result in lowered protection of women during the peri-ovulatory phase remains to be determined. Findings of cyclic changes in antibody levels during the menstrual cycle indicate that vaccine trials need to include analyses of genital tract secretions for all sexually transmitted vaccines, especially HIV. Further, in view of the large number or reports of adverse reactions to the US FDA Adverse Reaction Reporting Data base, the efficacy versus safety issues need to be further addressed.

2.4. Hormonal regulation of the FRT and the “Window of Vulnerability”

For successful fertilization and embryo survival, the immune system must therefore be modulated during mid-cycle of the menstrual cycle. Many studies have now been carried out to define the components of the immune system present in the FRT and to determine how these protect against pathogens, and how they are controlled by sex hormones (Fahey et al. 2011; Fahey, et al. 2008; Kutteh 2005; Wira et al. 2011).

A significant observation was made by Wira and Fahey when they asked the question: “From a viral perspective, what times during the menstrual cycle come closest to being optimal for infection?” By examining multiple immunological parameters the conclusion was made that within the FRT during a normal menstrual cycle, there is a period lasting 7–10 days when important components of innate, humoral, and cell-mediated immunity are suppressed by estradiol and/or progesterone, enhancing the potential for viral infection (Wira and Fahey 2008). As seen in Figure 1, onset of the “window of vulnerability” coincides with an increase in estradiol at about the time of ovulation. It has now been shown that immunological suppression occurs in both the upper and the lower FRT as an integral part of the physiological processes that underlie successful reproduction, and that this suppression coincides with recruitment of potentially infectable cells and upregulation of coreceptors on target cells that are essential for viral uptake (Wira and Fahey 2008). These observations have serious implications for increased susceptibility to STDs during the ovulatory-to-secretory phase of the menstrual cycle. Additionally there are now concerns that a variety of exogenous environmental and pharmaceutical compounds could dramatically alter normal immune function within the FRT. Whether these compounds alter susceptibility to external pathogens has yet to be adequately studied.

3. Potential of Environmental and Pharmaceutical Compounds to Alter the FRT Immune system

3.1. Endocrine Disruptors

Endocrine disruptors (EDs) are exogenous molecules that affect the normal action of hormones in the body including their synthesis, secretion, metabolism and transport (Brevini, et al. 2005; Cheek and McLachlan 1998; Cheek, et al. 1998; Fox 2004; Kavlock and Ankley 1996; Olea, et al. 1998). EDs include not only synthetic chemicals used in pharmaceutical or agricultural applications (e.g. pesticides, herbicides, plastics, therapeutic hormones) but also naturally occurring compounds present in the environment (e.g.

phytoestrogens). There are three types of endocrine disrupting mechanisms independent of ED concentration (Brevini et al. 2005). These include: (a) Binding to and irreversibly locking up the specific hormone receptor (hormone blocking); (b) Mimicking naturally occurring hormones (hormone mimicking); and (c) Acting through hormone-like pathways but initiating abnormal reactions (hormone triggering). While it is beyond the scope of this discussion to give a detailed overview of the many EDs (which will be discussed elsewhere in this special issue) it is important to appreciate their potential for altering the unique immune system within the FRT.

Altering the immune system by EDs could affect the ability to mount well-regulated immune responses to microbial and viral pathogens, vaccine antigens, allergens, as well as self and tumor antigens (Ahmed 2000; Chalubinski and Kowalski 2006; Forawi, et al. 2004). EDs can influence the synthesis of cytokines, immunoglobulins and cell mediators as well as modulating immune cell activation and survival via IL-4 production, Th1/Th2 balance and IgE production thus altering the balance between protection and susceptibility.

3.2. Effect of EDs on Reproduction and Development

The effects of EDs on mammalian reproduction and development are well studied. However, remarkably little is known about their effects on the development of the immune system, especially of the female reproductive tract. There have been numerous studies and reviews demonstrating effects of EDs on embryonic development and germ cell development and these are discussed in detail elsewhere. Table 5 summarizes the major classes of EDs, their mechanism of action and the reproductive and/or immune effects. Most bind to the estrogen receptor to either enhance or inhibit estrogenic effects.

Some EDs, particularly the phytoestrogens, have been shown to have some beneficial effects in humans (Cheek and McLachlan 1998; Cheek et al. 1998). Individuals living in regions where traditional diets are high in plant estrogens (e.g. soya meal) are reported to have lower incidences of breast and prostate cancer as well as atherosclerotic cardiovascular disease than people who consume a “Western” diet. More recent studies, however, have demonstrated that Genistein, an isoflavone estrogen, can negatively impact oocyte maturation and subsequent embryonic development (Chan 2009). However, the use of soya meal in infant formula is somewhat controversial and an expert panel concluded that more detailed studies are required to evaluate the long-term effects of phytoestrogen exposure and intake (Rozman, et al. 2006).

3.2 Effect of EDs on Immune Function of the FRT

While mechanisms for the effects of EDs on reproduction and development are not fully understood, even less is known about their effects on the immune system of the FRT. Table 5 summarizes some EDs, which are known to affect both the immune and reproductive systems. It will be important to determine their effects directly on the immune system of the FRT. For example, Heat Shock Proteins (HSPs) are known as “molecular chaperones which are essential for maintaining cell function by the prevention of protein misfolding resulting in protein aggregation (Fink 1999; Hartl and Hayer-Hartl 2002; Tsan and Gao 2009). They have also been proposed for use as biomarkers of environmental perturbation (Bierkens

2000). More recently, numerous HSPs have been implicated to play important roles in immune function including antigen presentation, activation of lymphocytes and macrophages, and activation and maturation of dendritic cells (Li, et al. 2002; Tsan and Gao 2004; Wallin, et al. 2002). With respect to the FRT, Papaconstantinou and colleagues (Papaconstantinou, et al. 2001) have shown that Bis-phenol A (BPA), an ED and a constituent of some plastics, resembles estradiol in its ability to induce increases in uterine heat shock protein levels, mainly hsp90α and glucose-regulated protein. They further demonstrated that both estradiol and BPA increased levels of HSPs at doses lower than those necessary for a significant increase in uterine weight (Papaconstantinou, et al. 2000). Given the role of HSPs in immune function, it can be hypothesized that EDs alter the ability of HSPs to modulate the immune system within the FRT.

Among EDs with deleterious side effects, DDT stands out as a result of its wide spread use to control malaria, a major cause of death in Sub-Saharan Africa. Its endocrine activity has been observed in mice and rat toxicological studies, and available epidemiological evidence indicates that these effects may be occurring in humans as a result of DDT exposure. DDT exposure damages the reproductive system, reduces reproductive success, semen quality, menstruation, gestational length, and duration of lactation (Chen and Rogan 2003; Roberts, et al. 2004; Rogan and Ragan 2003). In addition, exposure to DDT that would be needed in malaria control might cause preterm birth, which is a major contributor to infant mortality (Longnecker, et al. 2001; Rogan and Chen 2005). Given this association, it is imperative that future studies examine the effects of DDT and other chemicals on the FRT immune system. Given the long half-life of this molecule, up to 16 years, it will be important to study girls going into puberty who may have been exposed to these chemicals regularly throughout their lifetime.

As discussed in this review, the healthy immune system of women is important not only for general health but for prevention of STDs (including HIV) and disease progression. Hormone levels markedly affect immune function in the FRT. Thus the presence of EDs could have a substantial impact on normal immune protection. As the majority of women and children in Africa also have insufficient diets, their reproductive immune systems may be even at more risk for endocrine disruptors. In summary, it will be extremely critical in the coming years to more closely monitor the long term effects of these environmental and as well as industrial and pharmaceutical chemicals to determine if the population is being compromised and if there is an increase in susceptibility to STDs.

List of Abbreviations

FRT	Female Reproductive Tract
GM-CSF	Granulocyte macrophage colony stimulating factor
SLIPI	Secretory Leukocyte Protease Inhibitor
HβD2	Human β Defensin 2
MIP	Macrophage Inflammatory Protein

MCP-1	Monocyte Chemotactic protein-1
IL	Interleukin
TNF	Tumor Necrosis Factor
EDs	Estrogen Disruptors
HSP	Heat Shock Protein

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Research Highlights

We examine innate and adaptive immunity in the female reproductive tract (FRT).

We define the role of sex hormones in regulating FRT mucosal immunity.

Endocrine disruptors alter disease susceptibility in the FRT.

Reproductive health depends on understanding how endocrine disruptors work.

Information about endocrine disruptors will increase reproductive health.

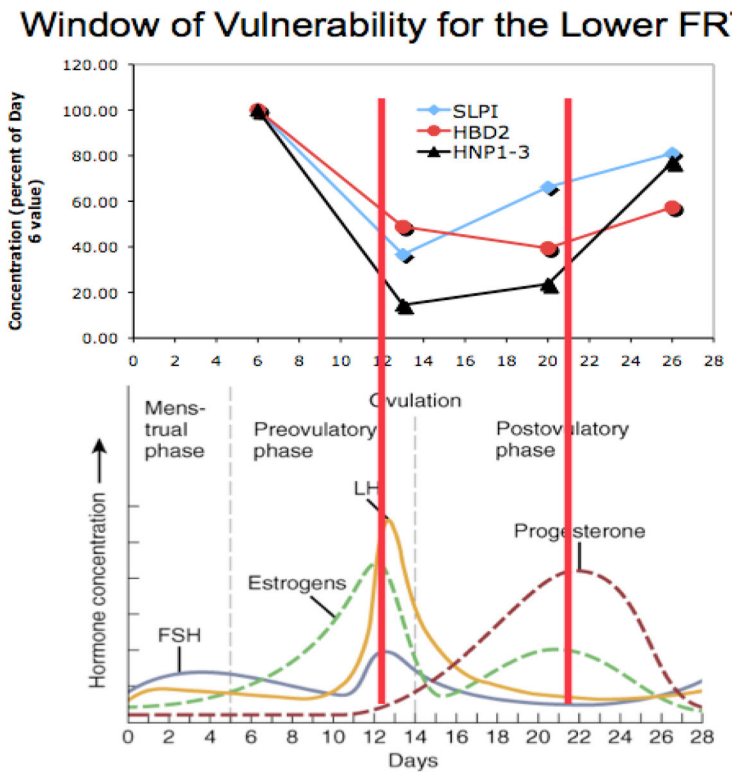

Figure 1. Hormonal regulation of the FRT and the "Window of Vulnerability"

During the window of vulnerability, which begins at ovulation and lasts 7–10 days, there is a marked drop aspects of the innate and adaptive immune systems as well as in several anti-HIV molecules that serve as major sententials in the innate immune system of the FRT. Innate immune antimicrobials that decrease in secretions from the lower FRT include human α-defensin-1-3 (HNP1-3), β-defensins 2 (HBD2), and secretory leukocyte protease inhibitor (SLPI). Adapted from (Keller et al. 2007).

Table 1

General Comparison of Innate and Adaptive Immunity in Vertebrates.

Innate (Non-specific Immunity)	**Adaptive (Specific Immunity)**
First line of defense	**Second line of defense**
Cellular and secreted components: cytokines, chemokines, microbicides	Humoral and Cell Mediated Protection
Response is antigen-independent	Response is antigen-dependent
Immediate response	Lag time between exposure and maximal response (antibody production)
Not antigen-specific	Antigen-specific (Antibody specificity)
Exposure results in no immunologic memory, but can be enhanced after exposure to antigen through effects of cytokines	Exposure results in immunologic memory

Table 2

General Functions of Major Immune Proteins involved in Mucosal Immunity and the Female Reproductive Tract.

Protein (Abbreviation)	Function	References
Cathelicidin	Produced by neutrophils, epithelial cells and macrophages; regulated by vitamin D	(Liu, et al. 2006)
Elafin/Trappin-2	Neutrophil elastase inhibitor with broad anti-microbial activity	(Wiedow, et al. 1990)
Granulocyte macrophage colony stimulating factor (GM-CSF)	Stimulates stem cell production of granulocytes and monocytes	(Caux, et al. 1992)
Human β-Defensin 2 (HBD2)	Produced by epithelial cells, has potent anti-microbial activity against gram-negative bacteria.	(Bensch, et al. 1995; Quayle, et al. 1998; Selsted and Ouellette 1995; Wira et al. 2010)
Interleukin 6 (IL6)	Both a pro- and anti-inflammatory cytokine; Induces differentiation of leukocytes.	(Heinrich, et al. 1998; Kishimoto, et al. 1995; van der Poll, et al. 1997)
Interleukin 8 (IL8)	Mediator of inflammatory responses	(Wolf, et al. 1998)
Macrophage Inflammatory Protein (MIP3α)	Recruits lymphocytes and neutrophils; binds and activates CCR6; Interfere with CCR5 and CXCR4 to inhibit HIV infection.	(Bleul, et al. 1996; Cocchi, et al. 1995; Schutyser, et al. 2003; Wira et al. 2010)
Monocyte Chemotactic Protein-1 (MCP-1)	Monocyte chemoattractant factor	(Marra, et al. 1999)
Transforming Growth Factor β (TGFβ)	Controls proliferation, cellular differentiation; anti-proliferative factor in normal epithelial cells	(Annes, et al. 2003; Shi and Massague 2003)
Tumor Necrosis Factor α (TNFα)	Cytokine involved in inflammation and cell apoptosis; Induce differentiation of leukocytes.	(Sedgwick, et al. 2000; Tracey and Cerami 1994)
Secretory Leukocyte Protease Inhibitor (SLPI)	Protects mucosa from neutrophil elastase; Anti-viral properties.	(King, et al. 2000; King, et al. 2003; McNeely, et al. 1995)

Table 3

Summary of Immune Cells in the Human FRT including Location and Hormone Receptor Properties.

Cell Type	Location in FRT (*Indicates high cell numbers)	Major Immune Functions (Innate Immunity, II Adaptive immunity, AI)	ERα	ERβ	PR	References
Macrophage	Vagina, ectocervix endocervix*, uterus* (lymphocyte aggregates), Fallopian tubes	II. Phagocytosis, kill microorganisms and infected cells; Antigen presentation	++++	+	++	(Fahey et al. 2011; Janeway 2004; Khan, et al. 2005; Murphy, et al. 2009; Wira et al. 2010)
Neutrophils	Vagina, ectocervix endocervix*, uterus*	II. Phagocytosis, Antimicrobial α Defensins	+++	++	–	(Fahey et al. 2011; Janeway 2004; Moreno, et al. 2003; Wira et al. 2010)
Dendritic Cell	Vagina, ectocervix, endocervix*, uterus*	II. Antigen presenting cells (links adaptive and innate immune systems)	++	++	+	(Fahey et al. 2011; Janeway 2004; Komi and Lassila 2000; Wira et al. 2010)
Uterine NK cell	Vagina*, ectocervix -*, endocervix, uterus	II. Nonspecifically kill virus infected and tumor cells.	–	+++	++	(Arruvito, et al. 2008; Fahey et al. 2011; Henderson, et al. 2003; Janeway 2004; Wira et al. 2010)
CD4$^+$ T Cells	Vagina, ectocervix, endocervix*, uterus*, Fallopian tubes *	AI. TH-1 cell mediated responses; IFN secretion – antiviral activity.	+++	++	+	(Fahey et al. 2011; Janeway 2004; Phiel, et al. 2005; Szekeres-Bartho, et al. 1990; Wira et al. 2010)
CD8$^+$ (Cytotoxic T lymphocyte)	Vagina, ectocervix, endocervix*, uterus*, Fallopian tubes*	AI. TH-1 cell mediated responses; Apoptosis of infected cells	+	+++	+	(Fahey et al. 2011; Janeway 2004; Phiel et al. 2005; Szekeres-Bartho et al. 1990; Wira et al. 2010)
B cell	Vagina, ectocervix, endocervix, uterus (lymphocyte aggregate core), Fallopian tubes	AI. TH-2 Humoral responses; Maturation into IgA/IgG secreting plasma cells	+	++++	–	(Fahey et al. 2011; Janeway 2004; Phiel et al. 2005; Sapino, et al. 2003; Wira et al. 2010)

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Table 4

Properties of Epithelial and Stromal Cells in the Human Female Reproductive Tract involved in Immune Function (ERα, Estrogen Receptor alpha; ERβ, Estrogen Receptor beta; PR, Progesterone Receptor; Hormone receptor levels premenopausal).

Organ	Cell Type	Hormone Receptors	Secreted Immune Modulators	References
Vagina	Stratified squamous	ERα++++ ERβ ± PR +++	IL6[#]; IL8[#]; SLPI[#]; HBD2[#]↓; Trappin-Elafin↓ HNP1-3[#]; lactoferrin[#]	(Fahey et al. 2011; Fahey et al. 2008; Herbst-Kralovetz, et al. 2008; Keller, et al. 2007; Murphy et al. 2009; Phiel et al. 2005; Schumacher et al. 1977; Schust, et al. 1996; Wira et al. 2010)
	Stroma	ERα ++ ERβ − PR +++		(Fahey et al. 2011; Fu, et al. 2003; Hodgins, et al. 1998; Pelletier and El-Alfy 2000)
Ectocervix	Stratified Squamous			(Wira et al. 2010; Yeaman, et al. 2003)
Endocervix	Columnar epithelium	ERα++ ERβ ± PR ++		(Fahey et al. 2011; Remoue, et al. 2003; Taylor and Al-Azzawi 2000)
	Stroma	ERα++ ERβ ++ PR +		(Fahey et al. 2011; Remoue et al. 2003; Taylor and Al-Azzawi 2000)
Uterus	Luminal Columnar Epithelium	ERα++++ ERβ ± PR +++	SLPI↑; IL6,8; MIP3α; Trappin-2/ Elafin; TNFα↓; HBD1,2↑; MIF↓; IL-6↓; IL-8↓	(Ghosh, et al. 2008; Ghosh, et al. 2010; Ghosh, et al. 2009; Jones, et al. 1995; Matsuzaki, et al. 1999; Pelletier and El-Alfy 2000; Taylor and Al-Azzawi 2000; Wira et al. 2010; Yeaman et al. 2003)
	Stroma	ERα++++ ERβ ± PR +++	HBD2, MIP3α	(Enmark, et al. 1997; Jones et al. 1995; Lecce, et al. 2001; Matsuzaki et al. 1999; Mylonas, et al. 2004; Pelletier and El-Alfy 2000; Taylor and Al-Azzawi 2000; Wira et al. 2010)
	Glandular epithelium	ERα++++ ERβ ± PR +++		(Fahey et al. 2011; Jones et al. 1995; Lecce et al. 2001; Matsuzaki et al. 1999; Mylonas et al. 2004; Pelletier and El-Alfy 2000; Taylor and Al-Azzawi 2000; Wira et al. 2010)
Fallopian Tube	Columnar ciliated	ERα± ERβ ± PR −		(Enmark et al. 1997; Fahey et al. 2011)
	Secretory columnar epithelium	ERα+++ ERβ +++ PR +++	SLPI↑; MIP3α; Elafin/Trappin-2	(Enmark et al. 1997; Fahey et al. 2011; Ghosh et al. 2008; Ghosh et al. 2010; Ghosh et al. 2009)
	Stroma	ERα+ ERβ ++ PR +		(Cretoiu, et al. 2009; Enmark et al. 1997; Fahey et al. 2011)

[*] Low during the proliferative stage of cycle and peak at time of ovulation;

[#] Levels drop significantly at mid-cycle.

Estradiol stimulates ↑; Estradiol inhibits ↓

Table 5

Examples of Different Classes of Endocrine Disruptors (EDs) Known to Alter Functions of Both the Reproductive and Immune Systems.

Compound/Source	Hormone Activity	Reproductive/Immune Effects	Reference
Zearalenone (ZEN)/fungal micotoxin in cereal crops	Binds estrogen receptors	Decreased fertility; altered Estradiol and Progesterone levels; Decrease in IL-8 synthesis by PMNs	(EFSA 2011; Marin, et al. 2010)
Bisphenol A (BPA)/poly-carbonate plastics, polystyrene	Estrogen agonist; androgen/ thyroid hormone antagonist	Accelerates puberty onset, altered estrous cyclicity (permanent estrus); Alters IFN-γ, immunoglobulin and interleukin production	(Fernandez, et al. 2009; Sawai, et al. 2003; Yoshino, et al. 2004; Yoshino, et al. 2003)
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), Industrial chemical	Binds aryl hydrocarbon receptor; anti-estrogenic	Inhibits CD4+ T cell differentiation into T helper effector cells; Inhibits uterine epithelial mitogenesis.	(Buchanan, et al. 2002; Marshall and Kerkvliet 2010)
DDT, organochlorine/insecticide	Binds estrogen receptor, antiandrogenic	Humoral immune suppression; stimulates the production of NO and proinflammatory cytokines; Reduces Lymphocytes; Adverse fertility effects	(Kim, et al. 2004; Lahvis, et al. 1995; Tiemann 2008)
Genistein, phytoestrogen	Binds Estrogen Receptor	Impairs oocyte maturation and embryonic growth; fish sex reversal; Increases in the activities of cytotoxic T cells and NK cells; Suppresses Humoral immunity and alters thymocyte development.	(Chan 2009; Guo, et al. 2001; Kiparissis, et al. 2003; Scholz and Gutzeit 2000; Vodkova, et al. 2008; Yellayi, et al. 2002)