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Review

# 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.



**Contents**



*Abbreviations:* FRT, female reproductive tract; GM-CSF, granulocyte macrophage colony stimulating factor; SLPI, secretory leukocyte protease inhibitor; HBD2, 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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## 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 that provide humoral and cell-mediated protection in response to a specific antigens present on pathogens. Unlike innate immunity, adaptive immunity results in long-term immunological memory (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, their progeny (e.g. memory B and T cells) will inherit the genes encoding the same antigen receptor specificity, thus giving long-lasting specific immunity as well as the ability to mount stronger immune 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 to the host. It is therefore crucial that the immune response is directed 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.

**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 |

### 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 have developed a complex and 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 at these sites 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 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 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.