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Microbiome, sex hormones, and immune responses in the reproductive tract: Challenges for vaccine development against sexually transmitted infections

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ABSTRACT

The female and male reproductive tracts are complex eco-systems where immune cells, hormones, and microorganisms interact. The characteristics of the reproductive tract mucosa are distinct from other mucosal sites. Reproductive tract mucosal immune responses are compartmentalized, unique, and affected by resident bacterial communities and sex hormones. The female and male genital microbiomes are complex environments that fluctuate in response to external and host-associated stimuli. The female vaginal microbiota play an important role in preventing colonization by pathogenic organisms. Sex hormones and their duration of exposure affect the composition and stability of the microbiome as well as systemic and mucosal immune responses. In addition to the characteristics of the pathogen they are targeting, successful vaccines against sexually transmitted pathogens must take into account the differences between the systemic and mucosal immune responses, the compartmentalization of the mucosal immune responses, the unique characteristics of the reproductive tract mucosa, the role of the mucosal bacterial communities, the impact of sex hormones, and the interactions among all of these factors.

1. Mucosal immunology of the reproductive tract

The female and male reproductive tracts are complex compartmentalized systems where immune cells, hormones, and microorganisms interact (Fig. 1). The characteristics of the reproductive tract mucosa are distinct from other mucosal sites [1]. Unlike the gastrointestinal and respiratory mucosae, they lack inductive mucoepithelial sites (e.g. Peyer's patches). As such, a significant proportion of IgG in genital secretions is derived from the local circulation. Sexually transmitted infections, especially chlamydia, can still elicit a strong local IgA and cell-mediated immune response [2–4]. Unlike most other mucosal sites (except the lower respiratory tract), the dominant immunoglobulin in genital secretions is IgG rather than IgA [5].

2. The female reproductive tract

The female reproductive tract may be divided into two parts: the lower (vagina and ectocervix) and upper (endocervix, uterus, fallopian tubes) tracts. The lower tract epithelium consists of multiple cell layers of stratified squamous epithelial cells that lack tight junctions allowing the movement of small molecules between the cell lines. The upper tract epithelium consists of a single tightly bound layer of columnar cells. The transition or transformation zone between the two has been shown to be a major effector and inductive site for cell mediated immune responses [6].

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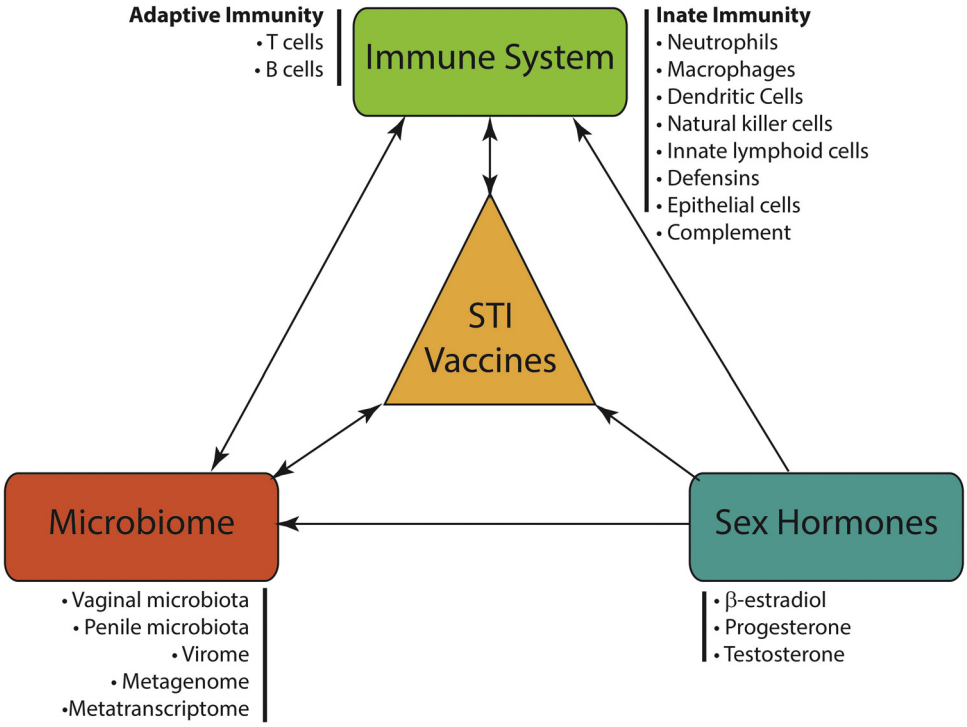

Fig. 1. There are multiple potential interactions between the immune system, sex hormones, the microbiome and vaccine efficacy. Some of these interactions may be bidirectional. Vaccines against sexually transmitted pathogens should take into account all of these factors.

2.1. Innate immunity

The epithelial surfaces of the female reproductive tract are covered with mucus which exhibits microbicidal activity [7]. The epithelial cells actively participate in the innate immune response [8,9]. In addition to their barrier function, they express pattern recognition receptors (PRRs) that mediate secretion of cytokines, chemokines, and antimicrobial peptides. They are also involved in antigen presentation. Neutrophils are distributed throughout the female genital tract, with the highest numbers in the upper tract. They are involved in phagocytosis, and the production of cytokines and antimicrobial peptides [10]. Antimicrobial peptides, which include defensins, chemokines, antiproteases, and enzymes play an important role in innate responses [11]. Macrophages and dendritic cells are similarly present throughout the female reproductive tract, with higher concentrations in the upper tract [12]. They are involved in phagocytosis and antigen presentation. In addition to their role in antigen presentation, dendritic cells have been shown to be critical players in inducing homing of effector and memory lymphocytes to mucosal tissues and in activation of memory T-cells [13,14]. These functions highlight their role as an important bridge between the innate and adaptive immune responses. Natural killer (NK) cells are widely distributed, but have a distinct phenotype from NK cells found in the systemic circulation [15]. They produce pro-inflammatory cytokines, promote macrophage activation, and cytotoxic T-cell generation. A newly described population of innate lymphoid cells (ILCs) play a role in regulating epithelial cell responses and maintaining local homeostasis. ILCs have been described in the skin, and in the intestinal and respiratory tracts (NK cells comprise a sub-group of ILCs) [16]. Several studies have highlighted the role of commensal bacteria in regulating the development, maintenance, and function of ILCs [17]. Far less is known about ILCs in the reproductive tract.

2.2. Adaptive immunity

The humoral (Th2) arm of the adaptive immune response in the genital tract consists mainly of IgG as well as secretory IgA (sIgA) [18]. The ratio of these antibodies varies by site. sIgA is characterized by enhanced neutralizing activity [19,20] and enhanced resistance to proteolysis [21]. Unlike IgG, sIgA does not activate complement. In addition to local production, there appears to be significant contribution of IgG from the systemic circulation to genital secretions [22,23]. The uterus is an important source of immunoglobulins in cervicovaginal secretions. T-lymphocytes are found in the stroma of the upper and lower reproductive tract as well as within epithelial cells (intraepithelial lymphocytes) [24]. CD8+ T-cells drive Th1 cell-mediated immunity that targets intracellular pathogens. CD4+ T-cells secrete IFN-γ and drive B-cell maturation. Th17 cells play a role in host defense against extracellular pathogens by mediating the recruitment of neutrophils and macrophages to infected tissues [25,26]. The female reproductive tract restricts entry of activated T-cells in the absence of inflammation or infection [27]. Consequently, parenteral vaccines that rely on cellular immunity to prevent STIs have not been successful. Recently, vaccines that elicit tissue-resident memory T-cell responses have been shown to be feasible [28,29] and may hold the key to a successful vaccination strategy against herpes simplex viruses and other sexually transmitted pathogens.

3. The male reproductive tract

In the male reproductive tract, keratinized stratified squamous epithelial cells cover the external surface of the penis. The male urethral orifice consists of a non-keratinized stratified squamous epithelium that transitions in the penile shaft to a pseudostratified columnar epithelium. The urethral epithelium expresses several membrane-associated mucins that act as a first-line of defense