Induction of mucosal immune responses in the human genital tract

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1. Introduction

Mucosae of the female and male genital tracts are the portals of entry for sexually transmitted diseases (STDs) of viral, bacterial, and parasitic origin; worldwide, \( \sim 120 \, 000 \, 000 \) cases of STDs are reported annually, but the true incidence is probably much higher. Infection with human immunodeficiency virus (HIV) is no exception: epidemiologic data indicate that worldwide, 70–90\% of all HIV infections are acquired by heterosexual transmission [1]. This route has the most rapidly rising incidence of new infections, especially among women, who are infected at higher rates than men. Thus, induction of immune responses at the major portals of entry of STD agents and HIV may be important for protection against these infections.

Studies performed in animal models and in humans have convincingly demonstrated that the mucosal and systemic compartments of the immune system display a significant degree of mutual independence [2]. Immunoglobulins (Ig) present in external secretions or systemic fluids are represented by molecules of different physicochemical and biological properties. In external secretions of humans and many mammalian species, the dominant Ig is secretory IgA (S-IgA), consisting of polymeric IgA (pIgA) with J chain, and secretory component (SC) derived from epithelial cells [3]. However, secretions of the female and male genital tracts differ from other external secretions (e.g., saliva or milk) as well as from plasma in the proportion of Ig isotypes and forms.

2. Immunoglobulins in secretions of the female genital tract

Studies of the mucosal immune system of the human genital tract have focused on female tissues and secretions, primarily due to the technically easy and ethically acceptable collection of secretions (vaginal washes and cervical mucus) and tissues (obtained during frequently performed hysterectomies and tubal ligations). Consequently, information on the levels of Igs during the menstrual cycle, their isotype distribution, physicochemical properties, and transport mechanisms, as well as the distribution of Ig-containing cells, antigen-presenting cells, and CD4+ and CD8+ cells in fallopian tubes, uterus, and vagina has been reported in considerable detail [4]. Moreover, Ig levels and isotypes display strong hormone-dependent variations, which are not as pronounced in other external secretions [5–7]. In human cervical mucus, there are higher levels of IgG than of IgA; this contrasts with other typical external secretions, such as saliva, tears, milk, and intestinal fluids, in which S-IgA is the dominant isotype.

Immunohistochemical examination of tissue sections or dispersed cells has indicated that the uterine endocervix contains higher numbers of Ig-secreting cells than the ectocervix, fallopian tubes, and vagina [8,9]. IgA- and IgG-secreting cells are dominant, and almost all IgA-producing cells contain J chain, a marker of synthesis of pIgA. Furthermore, the single-layered epithelial cells of fallopian tubes, uterus, endocervix, and ectocervical glands express SC which is essential for the selective transport of locally produced pIgA [10]. Thus, all structural and cellular components characteristic of the active transepithelial transport of pIgA are present. The mechanisms involved in the appearance of IgG in cervicovaginal secretions have not been elucidated. Ig produced locally and transported from blood by uterine tissues provide humoral immunity in the vaginal canal; hysterectomy greatly reduces Ig levels in the vagina [11].

Although the subepithelial connective tissue of the human vagina contains dispersed IgA- and J chain-positive plasma cells, the multilayered epithelial cells do not stain for SC [8,12]. Nevertheless, both IgA- and IgG-positive epithelial cells are frequently found on the luminal surface and dispersed among the multilayered epithelium. Such Ig-
positive cells contain both κ and λ Ig light chains and human serum albumin, but not C3 complement component, transferrin, or IgM. These data suggest that certain populations of vaginal epithelial cells can acquire, with some degree of selectivity, locally produced and plasma-derived proteins. However, mechanisms of Ig uptake are unknown, and the functional significance of intraepithelial Ig for the defense of the vaginal mucosa remains to be determined.

3. Immunoglobulins in male genital tract secretions

Although IgG, IgA, and IgM have been reported in both pre-ejaculate and seminal plasma [13–15], their relative levels have varied, perhaps due to differences in collection procedures, methods and standards used in Ig measurements, and the presence of proteolytic enzymes that are essential in liquefaction of semen but that also degrade especially IgM [16].

Higher levels of IgG than IgA are present in the ejaculate [14]. However, the pre-ejaculate contains more IgA than IgG [17]. On the basis of parallel measurements of the levels of plasma-derived proteins (e.g., albumin, transferrin) and Ig in split ejaculate, it appears that most IgG is derived from the circulation, while IgA, which is mainly represented by S-IgA, is of local origin [13,15].

Although Brandtzæg et al. [18], were unable to find Ig and SC expression in normal epididymis, seminal vesicles, or prostate by histochemical means and Northern blot analyses for SC mRNA, Anderson and Pudney [19] reported prominent SC staining in all of these tissues collected from HIV-infected men with genital tract inflammation. Furthermore, epithelial cells in Littre’s glands in the penile urethra displayed prominent SC staining in most specimens collected from apparently normal tissues [17,20]; plasma cells found in the vicinity of SC-positive epithelial cells stained prominently for IgA and J chain, or for IgG or IgM. Thus, the structural requisites for the operational assembly of S-IgA are present in the penile urethra but not in other segments of the male genital tract. Therefore, immunohistochemical and immunohistochemical data suggest that both plasma-derived and locally produced Ig are present in seminal fluid.

4. Common mucosal immune system (CMIS) and its compartments: relevance to the induction of immune responses in the genital tract

The cells engaged in the production of antibodies and, to a lesser degree, various populations of T cells destined for systemic and mucosal compartments display different tissue distribution, origin of precursors, and maturation patterns [21–23]. Approximately 70% of all Ig-producing cells in the human body are found in mucosal tissues; the remaining 30% are found mainly in the bone marrow (the most important source of plasma IgG and IgA) and in the spleen and lymph nodes [24,25]. In mucosae, some 80% of total Ig-producing plasma cells secrete IgA. Precursors of these cells originate in the IgA-inductive sites such as gut-associated lymphoid tissues (GALT) including Peyer’s patches (PP), solitary lymphoid nodules, and, probably rectal tonsils, bronchus-associated lymphoid tissues (BALT), and the nasal mucosa. Furthermore, external secretions collected from orally immunized individuals contain IgA antibodies specific for ingested antigens [26]. Cells derived from mucosal inductive sites home to the mucosal tissues and glands [27,28] where they terminally differentiate into plasma cells under the influence of locally produced cytokines [29]. Their product - polymeric IgA - is selectively transported through the epithelial cells into external secretions.

Lymphoid structures within or adjacent to mucosal surfaces may serve as additional IgA-inductive sites. These include an accumulation of lymphoid tissues strategically positioned in the oropharynx (known as Waldeyer’s ring) [30,31], and large intestine including rectum (rectal tonsil) [32,33]. Their potential participation in the CMIS as sources of precursor cells is suggested by the appearance of specific IgA antibodies in external secretions remote from the site of immunization (e.g., induction of specific IgA in the saliva of rectally immunized individuals [34]). Rectal immunization of women with inactivated influenza virus vaccine has resulted in the induction of low levels of IgA influenza-specific antibodies in the cervical secretions, but not in sera, within 28 days after vaccination [35]. Six months after rectal immunization, both IgA and IgG antibodies had been detected in cervical as well as vaginal secretions.

In another study, we evaluated the immune responses in genital tract secretions of women immunized rectally or orally with an attenuated Salmonella typhi Ty21a vaccine [36]. Specific antibody-secreting cells were detected in the circulation of both groups of women, and almost all such cells expressed the mucosal homing receptor, α4β7, whereas L-selectin, the homing receptor for peripheral lymph nodes, was expressed only on approximately one-third of peripheral blood cells. There were, however, differences in levels of specific antibodies in various external secretions: oral immunization elicited a more pronounced humoral response in saliva and vaginal washes, while rectal immunization induced higher levels of specific antibodies in rectal secretions, tears, and nasal fluid. Interestingly, oral immunization followed by rectal administration appeared to be the most effective combination of vaccination routes for the induction of S-IgA antibodies in female genital tract secretions (Kutteh et al., unpublished results).

One of the most remarkable recent developments in mucosal immunology concerns the relative importance of inductive sites associated with the nasal cavity and the induction of immune responses in the female genital tract.
The presence of antibodies to Neisseria gonorrhoeae in the genital tract secretions as a result of STD infections has been examined. The response to gonococcal infection is very modest and displays no relation to previous infection that would suggest the development of immune memory [62,63]. These findings accord with the well-known fact that gonorrhea can be contracted repeatedly with little or no evidence for enhanced resistance as a result of repeated exposure. Undoubtedly numerous factors contribute to the limited immune response developed in human gonorrhea, but among them is likely to be the absence in the genital tract of specialized lympho-epithelial tissues akin to the Peyser's patches of the intestine and similar structures elsewhere, which are considered to be the principal inductive sites of the mucosal immune system. It is clear that paternally derived fetal histocompatibility antigens can induce antibody responses in utero, and several studies of genital tract immunization have shown that antigens such as cholera toxin or live attenuated viruses can induce local antibody responses in experimental animals or humans [64–70]. However, in general the responses are not disseminated to other mucosal sites or the serum, and are usually inferior to those induced by the same immunogen administered orally or intranasally.

5. Systemic immunization and antibody responses in genital tract secretions

Because antibodies of the IgG isotype are dominant in both male and female genital tract secretions and are largely of plasma origin, the effectiveness of the systemic route of immunization has been evaluated in several studies. Injection of tetanus toxoid [53] or inactivated influenza virus vaccine [35] induced antigen-specific IgG antibodies in vaginal and cervical secretions. Systemic immunization of males with an experimental gonococcal vaccine induced antibody responses in utero, and several studies of genital tract immunization have shown that antigens such as cholera toxin or live attenuated viruses can induce local antibody responses in genital tract secretions are in progress in our laboratory [52].

Intranasal immunization of women with recombinant CTB is of particular importance for induction of antibody responses in the genital tract secretions: doses of 100 and 1000 µg of CTB were highly effective for stimulating relatively high levels of specific antibodies [37]. Studies of intranasal immunization with bacterial and viral vaccines and induction of antibodies in genital tract secretions are in progress in our laboratory [52].

6. Responses of the genital tract to infection and immunization

Despite their obvious importance, relatively few studies have been performed on the immune responses developed in the genital tract secretions as a result of STD infections. The presence of antibodies to Neisseria gonorrhoeae in female and male secretions has been amply demonstrated [56–61], but our recent quantitative analyses indicate that the response to gonococcal infection is very modest and displays no relation to previous infection that would suggest the development of immune memory [62,63]. These findings accord with the well-known fact that gonorrhea can be contracted repeatedly with little or no evidence for enhanced resistance as a result of repeated exposure. Undoubtedly numerous factors contribute to the limited immune response developed in human gonorrhea, but among them is likely to be the absence in the genital tract of specialized lympho-epithelial tissues akin to the Peyser's patches of the intestine and similar structures elsewhere, which are considered to be the principal inductive sites of the mucosal immune system. It is clear that paternally derived fetal histocompatibility antigens can induce antibody responses in utero, and several studies of genital tract immunization have shown that antigens such as cholera toxin or live attenuated viruses can induce local antibody responses in experimental animals or humans [64–70]. However, in general the responses are not disseminated to other mucosal sites or the serum, and are usually inferior to those induced by the same immunogen administered orally or intranasally.

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References


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