Published in final edited form as:
Am J Reprod Immunol. 2014 August ; 72(2): 219–227. doi:10.1111/aji.12202.

Mucosal Correlates of Protection in HIV-1-Exposed Seronegative Persons

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Abstract

Resistance to HIV-1 infection in HIV-1-exposed seronegative (HESN) persons offers a promising opportunity to identify mechanisms of "natural" protection. Unique features of the mucosa in particular may contribute to this protection. Here we highlight several key issues pertaining to the mucosal correlates of protection in HESN persons, including humoral immune responses, mechanisms of mucosal HIV-1-neutralization, immune cell activation, and role of the microbiota in mucosal responses. We also discuss mucosal model systems that can be used to investigate the mechanisms of resistance in HESN subjects. A clear understanding of the mucosal correlates of protection against HIV-1 in HESN persons will provide critical new insights for the development of effective vaccine and microbicide strategies for the prevention of HIV-1 transmission.

Keywords

cervicovaginal lavage; genital; HESN; immune activation; mucosal secretion; microbiota

Introduction

Most HIV-1 infections are acquired through the mucosal surface of either the genital tract or the gastrointestinal tract, two immunologically distinct mucosal sites. Although the rate of HIV-1 transmission across mucosal surfaces is low, thousands of mucosal transmissions occur each year, relentlessly fueling the global AIDS epidemic. However, despite frequent or repeated mucosal exposure, some persons appear to be naturally resistant to HIV-1 infection. Resistance to the virus in HIV-1-exposed seronegative (HESN) subjects provides a unique opportunity to elucidate mechanisms of "natural" protection.

Since natural immunity to HIV-1 was reported in seronegative sexual partners of HIV-1-positive men in 1989 [1, 2], identification of HESN cohorts has expanded to include commercial sex workers, men who have sex with men, discordant couples, highly exposed intravenous drug users, infants born to HIV-1-infected mothers, and hemophiliacs [3, 4].

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Investigation of HESN cohorts has revealed potential correlates of protection [5, 6], including the presence of (a) specific alleles and polymorphisms such as the CCR5Δ32 deletion allele [7], CCR2-I-allele [8], polymorphisms in MHC [9, 10], SDF-1 [11] and IRF-1 [12]; (b) innate defense molecules such as APOBEC3G [13], defensins [14, 15] and CD8 antiviral factor [16, 17]; (c) innate immune responses, including natural killer cell responses [18–21]; (d) adaptive immune responses, including the presence of HLA- [22–24], CD4- [23–26] and CCR5-specific antibodies [26], HIV-1-specific IgA [26–28] and/or IgG [24] antibodies; and (e) HIV-1-specific helper and cytotoxic T lymphocytes [22, 23, 29–33]. Although the level of exposure, cohort size, and detection assays vary, it has become apparent that natural resistance to HIV-1 infection in HESN persons is likely multi-factorial.

The mechanism of protection in HESN persons has not been elucidated, although progress has been made in the HESN field, and information regarding the general correlates of protection in HESN cohorts has been provided [3–6, 34–36]. Here we provide a focused review of key HESN studies and highlight the mucosal correlates of protection. We also emphasize controversies and issues that warrant future study, including secretory humoral responses, mechanisms of mucosal HIV-1-neutralization, local immune cell activation and the role of the microbiota, in HESN persons.

Mucosal humoral immune responses in HESN persons

Studies of humoral immune responses in HIV-1-infected women have shown that high levels of HIV-1-specifc IgG antibodies are present in sera but that HIV-1-specific IgA antibodies, which are present in all body fluids, are detected less frequently and at lower levels. In addition, cervicovaginal lavage (CVL) frequently contains HIV-1-specifc antibodies of the IgG isotype at higher concentrations than antibodies of the IgA isotype. Also, low levels of HIV-1-specific IgA antibodies are more frequently detected in vaginal washes and semen than in other external secretions in HESN subects [37–45].

In HESN cohorts, the presence and levels of HIV-1-specific antibodies in sera and external secretions is controversial. In a multicenter analysis, sera and CVL from 41 HESN Tanzanian sex workers were analyzed in a blinded fashion in six laboratories. In 41 HESN plasma samples, low levels of IgG antibodies to gp41 peptide were detected in one to five samples in three laboratories, and low levels of IgA antibodies to gp41 were detected in four samples in only one laboratory. In 41 CVLs, markedly reduced levels of HIV-1-specific IgG were detected in five to eight washes by ELISA, but not by chemiluminescence-enhanced Western blot, in three of six laboratories. No HIV-1-specific IgA antibodies were detected in the sex workers [46]. In agreement with this multicenter analysis, three independent studies reported the absence of HIV-1-specific IgA in genital secretions [47–49]. In contrast, HIV-1-specifc IgA antibodies have been detected in other HESN cohorts [27–29, 40–42, 50–54].

One explanation for the differences in anti-HIV-1 antibody levels in the above studies could be the use of different criteria to define HESN. In July 2010, HESN (or HIV-1-Exposed Seronegative) was accepted as the general term for the field at the Workshop of HIV-1 Exposed and Resistant Subjects held in Rockville, Maryland [3]. HESN was defined as a person lacking both HIV-1-specific IgG and evidence of infection in the setting of frequent

HIV-1exposure. Based on this definition, some subjects in previous studies would have been excluded. The variation in anti-HIV-1 antibody levels also could be due to differences in the mode of transmission, levels of exposure, duration of seronegative status, epidemiological background of the HESN subjects and experimental methodology. These potential causes of variable HIV-1-specific antibody levels warrant prospective study. More definitive diagnostic criteria and methodologies should facilitate such future studies.

Mechanisms of HIV-1-neutralization in the mucosae of HESN subjects

The ability of antibodies to prevent SHIV infection in mucosa-applied virus challenge has been demonstrated in the macaque model [55–58]. In this model, systemically administered monoclonal virus-neutralizing antibodies protected animals against vaginally inoculated virus [56–58]. Because transudation of circulating antibodies, particularly of the IgG isotype, contribute to the Ig pool in female genital secretions, passively administered antibodies likely protected the animals by interaction with the virus in the vaginal lumen, thereby preventing virus entry. This interpretation is supported by the protective effect of antibodies applied intravaginally prior to virus challenge [55]. The administered antibodies were of the IgG isotype; IgA and IgM antibodies were not studied in this model.

HIV-1-neutralizing activity has been detected in mucosal secretions [28, 40, 53, 59–64]. This activity has been attributed to both antibodies such as IgA and innate factors including secretory leukocyte protease inhibitor (SLPI), lysozyme, lactoferrin, RNases and antibodies to HLA, CD4, and CCR5 [28, 40, 53, 59–65]. Consequently, to assess the capacity of secretory antibodies to neutralize HIV-1, the Igs must be isolated or selectively removed from the secretions. In a Tanzanian study [46], HIV-1-neutralizing antibodies were detected at highly variable titers in the sera of the majority of 26 HIV-1-infected women, whereas only one sample among the 41 HESN sera displayed virus-neutralizing activity, which was detected at a low level. In CVL, virus-neutralizing activity was detected in 11 of the 26 HIV-1-infected women and 19 of 41 HESN women. Furthermore, in CVL from 41 HESN women, no HIV-1-specific IgA was detected, and HIV-1-specific IgG was detected in only 5 to 8 samples, depending on the laboratory in which the antibodies were measured. These findings suggest that factors other than HIV-1-specific Ig have neutralizing activity in the secretions of HESN women [46]. Further investigation is clearly needed to determine the mechanism of HIV-1 neutralization in the mucosa and identify the factor (innate humoral molecule, IgG, and/or IgA) that mediates the neutralizing activity, particularly in relevant mucosal cells and tissue. Studies also are needed to determine whether human CVL and rectal secretions from HESN women block HIV-1 entry into mucosal lamina propria target cells in order to elucidate whether the protective effect of such antibodies is due to the blockade of virus entry or virus neutralization and to determine the underlying mechanism of the blockade and/or neutralization.

Although controversial, the presence of HIV-1-specific IgA antibodies in genital secretions of HESN women has been assumed to provide protection via inhibition of transcytosis and neutralization. However, the function of such antibodies has not been rigorously investigated. The protective effect of secretory antibodies could depend on virus neutralization or the blockade of virus entry and dissemination (translocation through the

mucosa). For example, the ability of non-neutralizing antibodies to inhibit HIV-1 replication in macrophages and immature DCs has been reported [66]. In the murine transplantation model of intestinal rotavirus infection, non-neutralizing antibodies of the IgA isotype also are protective [67].

Mucosal immune activation in HESN persons

Immune activation plays an important role in AIDS pathogenesis. Available evidence indicates that immune activation is a major cause of immune dysfunction in patients with chronic HIV-1 infection and macaques with SIV infection [68–70]. The potential factors that induce immune activation include the direct effect of HIV-1/SIV on epithelial cells and T cells, the host immune response to HIV-1/SIV, the depletion of $CD4^+$ regulatory T cells whose normal function is to suppress immune activation, the translocation of microbial products such as lipopolysaccahride (LPS) from the intestinal lumen to the circulation, bystander activation of lymphocytes and possibly other factors [68–70]. Immune activation is reflected in the increased number of $CD8^+$ T cells, increased activation and/or apoptosis of $CD4^+$ and $CD8^+$ T cells, B cells, NK cells and monocytes [71–73], increased production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-18 and TNF-α [74–76], and increased MIP-1α, MIP-1β, RANTES, ICAM-1 and other chemokines [77]. The pivotal role played by immune activation in AIDS pathogenesis is further supported by studies in the SIV primate model [68, 78]. SIV-infected African green monkeys and sooty mangabeys, the natural hosts of SIV, lack immune activation and do not develop immunodeficiency disease, whereas SIV-infected rhesus macaques display strong T cell activation and develop AIDS [78].

The role of immune activation in the natural resistance of HESN persons to HIV-1 infection is the subject of debate. The widespread HIV-1 epidemic in Africa has been linked to the immune activation of $CD4^+$ T cells in the genital tract and in the peripheral blood of African subjects [71–73, 77]. Low level $CD4^+$ T cell activation has been reported in HESN cohorts in the Central African Republic [79], Senegal [80], Kenya [81], as well as Amsterdam [82]. The low level $CD4^+$ T cell activation reported was associated with low susceptibility to HIV-1 infection. A gene expression analysis of blood samples from a HESN cohort of commercial sex workers in Nairobi, Kenya reveals a signature pattern reminiscent of a lowered immune activation state [83]. A distinct cytokine and chemokine profile in HESN genital mucosa [84], as well as blunted production of both pro-inflammatory cytokines (including IL-17 and IL-22) and β-chemokines in the cervix and blood of HESN subjects [85], also supports the immune quiescence model of protection. In preliminary work, we have shown that HESN CVL down-regulates mRNA levels of the pro-inflammatory cytokines IL-1β and IL-6 in peripheral blood mononuclear cells compared with CVLs from HIV-1-infected and uninfected women (unpublished data). However, a number of other studies have reported increased levels of immune activation in HESN populations [86–89].

The role of mucosal integrity in defense against primary HIV-1 transmission is well established. Importantly, mucosal integrity is impaired during local inflammation. Consequently, increased HIV-1 transmission may occur due to disrupted mucosal epithelium caused by infection and immune activation, increased numbers of target $CD4^+$ T cells associated with the inflammation, and/or elevated levels of local proinflammatory cytokines

during inflammation and/or infection [90]. In HESN women, factors in the cervicovaginal and rectal secretions, including IgA, may modulate these processes, regulate the phenotype of target cells, and limit local inflammation, thereby reducing the host's susceptibility to HIV-1 and contributing to natural resistance to HIV infection.

Importantly, IgA could function as a non-inflammatory Ig isotype because IgA does not activate complement (C) but effectively inhibits C-activation mediated by antigen-IgG/IgM complexes [91]. Brandtzaeg and Tolo [92] showed that formation of immune complexes in mucosal tissues between mucosa-applied antigen and plasma-derived IgG or IgM antibodies results in local C activation, influx of neutrophils, epithelial barrier damage and consequently enhanced absorption of by-stander antigens. In contrast, complexes formed with non-C-activating IgA do not display these harmful activities. Thus, the levels and Ig isotype distribution of antibodies to mucosal antigens may play a critical role in the absorption of biologically active molecules such as LPS and other bacterial products, and subsequent lymphocyte activation and cytokine production, leading to enhanced susceptibility to HIV-1. The genital and gastrointestinal tracts display physiological and immunological uniqueness with marked and distinctive differences in the dominant distribution and levels of Ig isotypes, as well as the phenotypes of lymphocytes, macrophages, and DCs. Furthermore, different levels and types of bacterial species colonize the vaginal and rectal mucosae and provide antigens to form immune complexes. These complexes may further compromise mucosal integrity, allowing absorption of by-stander antigens. Thus, the Ig fraction in the cervicovaginal and rectal secretions may contribute to HIV-1 transmission and infection. In HESN women, both the Ig fraction and the non-Ig fraction of cervicovaginal fluid may differentially regulate the phenotype of target cells and limit local inflammation, potentially contributing to natural resistance to HIV-1 infection. In this connection, human breast milk [93–95] and saliva [59–61] have been shown to contain innate factors with anti-inflammatory and/or anti-HIV-1 activities.

Mucosal model systems in the study of HESN subjects

As discussed above, HIV-1-sepecific humoral and T-cell-mediated responses have been identified in HESN subjects, but whether these responses provide protection or constitute a marker for exposure is unclear. To address this issue, appropriate mucosal models and relevant mucosal secretions are critical. Such model systems also will be useful to define the role of the tissue microenvironment in genital and rectal mucosa in natural resistance of HESN populations.

The genital and gastrointestinal tracts display physiological and immunological uniqueness with marked and distinctive differences in inductive sites, the distribution and levels of Ig isotypes [96], as well as the composition and phenotypes of lymphocytes, macrophages, and DCs. These potentially confounding features can be addressed using isolated mucosal mononuclear cells and human mucosal explants such as the vaginal [97], rectal [98], and intestinal [97, 99] explant systems, which we and others have developed and which recapitulate the mucosal microenvironment [97, 99–101]. Human mucosal explant models are highly relevant, allowing a range of cells, including epithelial cells, DCs and T cells, to be studied in a more physiological setting. Using a vaginal explant model, we have shown that HESN

CVL inhibited HIV-1 entry and DC transport of HIV-1 through vaginal mucosa (unpublished data).

Mucosal microbiota in HESN persons

The microbiota of each mucosal compartment is characterized by distinct communities of bacteria and viruses that participate in the regulation of the immune system and host protection against certain pathogens [102–106]. Recently, the genital and gastrointestinal tract microbiota have been increasingly recognized as important factors in HIV-1 infection [107, 108]. The presence of genital tract infections such as bacterial vaginosis (BV), trichomoniasis, chlamydia, gonorrhea, syphilis, human papilloma virus, and human simplex virus increase the risk of HIV-1 infection [109–113]. In HIV-1-infetced women, vaginal microbiota display higher diversity and skew toward a BV-associated microbiota [114–116]. Importantly, vaginal *Lactobacillus* species (*L. crispatus* and *L. jensenii*) are associated with lower risk of genital HIV-1 shedding, whereas the presence of certain BV-associated species, including BVAB3, *Leptotrichia* and *Sneathia*, may increase that risk [117]. These findings suggest that the mucosal microbiota could potentially contribute to the natural resistance to HIV-1 in HESN subjects. In this connection, Schellenberg and colleagues [118, 119] reported that HIV-1-infetced women are more likely to be diagnosed with BV compared with HESN and HIV-1-negative women, that some HIV-1-infetced women have distinct vaginal bacterial profiles dominated by *Escherichia coli* and that similar proportions of HESN and HIV-1-negative women have BV. However, whether mucosal microbiota contribute to the natural resistance characteristic of HESN populations is not known and warrants careful investigation.

Concluding remarks

Natural resistance to HIV-1 infection in HESN subjects is likely multi-factorial. Identifying the correlates, especially mucosal correlates, of protection in HESN persons will provide new direction(s) for the development of effective vaccine and microbicide strategies for the prevention of HIV-1-transmission. However, many controversial issues remain to be addressed, and new areas to be explored will undoubtedly emerge. Elucidating the mucosal humoral responses, mechanisms of mucosal HIV-1-neutralization, immune cell activation and the influence of mucosal microbiota are the beginning in the long investigative road that will lead to identification of the relevant mucosal correlates of protection in HESN persons.

Acknowledgments

This work was supported by National Institutes of Health grants AI093151 and AI106395, UAB Center for AIDS Research (CFAR) and Comprehensive Cancer Center Development Core Grant (RS); and AI083127, RR-20136, DK064400, and the Research Service of the Veterans Administration (PDS).

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