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Friend or Foe – Innate sensing of HIV in the female reproductive tract

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Abstract

The female reproductive tract (FRT) is a major site for human immunodeficiency virus (HIV) infection. There currently exists a poor understanding of how the innate immune system is activated upon HIV transmission and how this activation may affect systemic spread of HIV from the FRT. However, multiple mechanisms for how HIV is sensed have been deciphered using model systems with cell lines and peripheral blood-derived cells. The aim of this review is to summarize recent progress in the field of HIV innate immune sensing and place this in the context of the FRT. Because HIV is somewhat unique as an STD that thrives under inflammatory conditions, the response of cells upon sensing HIV gene products can either promote or limit HIV infection depending on the context. Future studies should include investigations into how FRT-derived primary cells sense and respond to HIV to confirm conclusions drawn from non-mucosal cells. Understanding how cells of the FRT participate and effect innate immune sensing of HIV will provide a clearer picture of what parameters during the early stages of HIV exposure determine transmission success. Such knowledge could pave the way for novel approaches for preventing HIV acquisition in women.

Keywords

HIV; Innate sensing; FRT; Inflammation; Transmission

Introduction

The primary routes of HIV transmission in humans are through the mucosal surfaces of the genital or gastrointestinal tract. Today, women worldwide are more likely to be infected than men, and transmission to women through the female reproductive tract (FRT) accounts roughly for one-third of all HIV transmission events [1]. Upon deposition into the FRT, HIV must pass the mucosal epithelium to gain access to HIV-permissive cells in the underlying lamina propria [2]. The encounter between HIV and these cells, as well as non-permissive

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cells, can trigger innate immune activation through intrinsic pathogen recognition receptors (PRRs). PRRs, expressed on a variety of cell types in particular innate immune cells, sense pathogen-associated molecular patterns (PAMPs) from invading microorganisms [3-5], which in the case of HIV is primarily the single-stranded RNA genome or the viral reverse-transcribed DNA intermediates initially produced in the cell cytoplasm of infected cells [6]. This sensing triggers production of antiviral and inflammatory factors such as type I and III IFNs that increase local inflammation and cell death. Although immune activation is generally beneficial for protection against mucosal pathogens, whether this is also the case for HIV-1 is unclear. On the one hand, innate immune responses may restrict the ability of HIV to replicate in mucosal tissues by upregulating antiviral factors. On the other hand, inflammation can create a favourable environment for HIV to propagate itself by recruiting HIV-permissive cells such as T cells, macrophages and dendritic cells (DCs) [7-10]. It is likely that the type of inflammatory response, as well as when it is elicited, will determine whether it is effective at restricting HIV transmission.

The mechanisms by which HIV is sensed in the FRT is poorly understood due to the limited number of studies done on cells from this tissue compartment, but conceivably includes mechanisms similar to those worked out from studies using cell lines and primary cells derived from human blood and non-mucosal tissues. However, because the FRT is a distinct environment that is highly hormonally responsive and designed to be tolerant of semen components, there are likely also unique aspects of HIV sensing in this tissue that are not observed at other sites. In this review, we discuss recent progress in the field of HIV innate immune sensing, bring up some concepts regarding the role of HIV sensing in the FRT and how it can influence viral transmission, and discuss the need for future sensing studies to incorporate the use of FRT-derived primary cells in the context of the mucosal environment.

Molecular players involved in HIV sensing

Each HIV particle carries two single-stranded RNA genomes, which can be recognized as PAMPs by PRRs. Although it has been demonstrated that the cytosolic RNA sensor RIG-I [11, 12] and the endosome-localized toll-like receptor (TLR) 7 [13-15] can sense HIV RNA, the mechanistic details of this process and outcome of sensing are not well understood. In contrast, much more is understood about sensing of HIV DNA products, which are generated when the RNA genome is reverse-transcribed into proviral DNA following viral entry [16-21]. It is widely debated how and when reverse-transcribed products of HIV are sensed [22, 23]. In some cases, cloaking of the reverse-transcribed DNA intermediates by the viral capsid seems to protect against sensing by cytoplasmic PRRs [18, 19], whereas in other cases cytoplasmic HIV single-stranded DNA (ssDNA), RNA:DNA hybrids or dsDNA potently induce innate immune activation [16, 17, 22, 24-26]. Whether nuclear pre-integration complexes containing HIV DNA can be sensed is not known. Studies conducted in primary T cells, macrophages, and DCs have demonstrated that at least three host proteins may act as the PRRs for HIV DNA fragments: Interferon Inducible factor 16 (IFI16) [17, 26], Cyclic GMP-AMP synthase (cGAS) [16, 17], and Polyglutamine binding protein 1 (PQBP1) [21]. In the next sections we summarize in detail the molecular mechanisms by which each of these nucleic acid sensors (RIG-I, TLRs, IFI16, c-GAS, and PQBP1) detect HIV and activate innate immune responses.

RIG-I and Toll-like Receptor sensing

RNA viruses are generally sensed by TLR3, TLR7, TLR8, or members of the RIG-I like receptor family. These sensors are abundantly expressed on myeloid and lymphoid cells, both of which reside within the mucosa of the FRT and can serve as targets for HIV infection [27]. Of the RNA sensors, only TLR7 and RIG-I have been demonstrated to sense the HIV ssRNA genome. When primary human macrophages or PBMCs are stimulated with genomic HIV ssRNA, delivered to the cells by liposomal complexes, it is possible to observe RIG-I activation. This then initiates signalling through the MAVS pathway, which eventualy induces the secretion of type I IFN and inflammatory cytokines such as CXCL10, IL6, and TNF-α [11]. However, during infection of permissive cells with HIV, viral protease downregulates expression of RIG-I through a lysosome-dependent pathway, thereby inhibiting RIG-I-mediated sensing of HIV RNA [12]. Nonetheless, viral evasion of the RIG-I-mediated sensing pathway may be overcome when RIG-I is activated by its natural ligand 5′-ppp-dsRNA prior to HIV infection [28]. This protection can be attributed to IFN induction and upregulation of multiple ISGs within the cells. But because the RIG-I sensor needs to be activated prior to HIV infection to protect cells against infection, it is likely that RIG-I sensing during HIV transmission only plays a minor role in innate immune-mediated control of the virus.

In contrast, there is compelling evidence for TLR7-mediated sensing of HIV during active infection. TLR7 senses extracellular nucleic acids following their uptake into endosomal compartments. As such, cells not efficiently infected by HIV can induce a strong IFN response following exposure to the virus [29]. In both *in vitro* and *in vivo* models, TLR7-mediated induction of IFN following HIV infection is largely mediated by plasmacytoid DCs (pDCs) [30-35]). pDCs are thought to be largely refractory to productive infection by HIV, even though they express CD4, CCR5 and CXCR4 [36]. This refraction is thought to be due to high expression of the host restriction protein SAMHD1, a phosphohydrolase that by depleting the deoxyribonucleotide pool limits HIV reverse transcription [37, 38]. pDCs commonly reside in mucosal tissues, and studies from non-human primates demonstrated that SIV challenge induces migration of pDCs from the bone marrow to mucosal tissues, including the gut and FRT, in a manner coincident with upregulation of the mucosa-homing marker α4β7 on these cells [39, 40]. Furthermore, infiltration of pDCs into the FRT of macaques occurs following repeated vaginal exposure to SIV [41]. In addition to pDCs, other TLR7-expressing cells are present in the FRT include monocytes, macrophages, and DCs [42-45]. These cells may conceivably also participate in sensing of HIV RNA during active infection.

Within the FRT, TLR7 is widely expressed in the fallopian tubes, uterine endometrium, cervix, and ectocervix [46], suggesting that HIV RNA can theoretically be sensed throughout the FRT. Counterintuitively, intravaginal application of rhesus macaques with a TLR7 agonist during SIV infection resulted in higher viral loads compared to animals that were inoculated with SIV in the absence of the agonist [47]. One potential explanation for this phenomenon comes from a recent study, demonstrating that CD4+ T cells and innate immune activation through TLR7 induces a state of immunological CD4+ T cell anergy that increases permissiveness to HIV infection [48]. Using RNAi and TLR7 antagonists, the

authors demonstrated that inhibiting TLR7 signalling on CD4+T cells diminishes HIV infection, and *ex vivo* treatment of CD4+T cells from HIV-infected patients with TLR7 antagonists decreases viral outgrowth and production [48]. Conversely, stimulation of TLR7 on CD4+ T cells renders these cells more permissive to HIV infection, and patient-derived HIV-infected cells stimulated with TLR7 agonists potently reactivate HIV.

Of note, TLR7 may not be the only TLR capable of sensing HIV. TLR2 and 4 may also serve as sensors of HIV due to their ability to recognize HIV gp120 surface proteins [49]. This recognition can lead to inflammatory cytokine production in the FRT, as exposure of polarized genital epithelial monolayers to gp120 induced proinflammatory cytokines, including TNF-α and IL-8. Interestingly, this inflammatory response disrupted tight junctions and increased transcellular passage of components across the monolayer [49], suggesting that innate recognition of envelope may promote HIV transmission by disrupting the epithelial layer of the FRT.

Interferon inducible factor 16 (IFI16)

Ifi16 is an interferon-stimulated gene that encodes a multifaceted protein found in a wide variety of cells including epithelial cells, lymphoid cells, myeloid cells, and some hematopoietic cells [50]. It is expressed in both the nucleus and cytosol and has the capacity to shuttle between these two compartments in a manner regulated by acetylation [51, 52]. It is part of the AIM2-like family, whose members are characterized by structural motifs containing N-terminal protein-protein domains (PYRIN) and C-terminal DNA binding domains (HIN-200). IFI16 contains two HIN-200 domains (HIN-A and HIN-B) which recognize and physically bind DNA [53] that exhibit a variety of structural patterns [17, 53-56]. The affinity of the HIN domains for DNA is high (K_D in nano-molar range), and upon binding IFI16 undergoes filamentous clustering [55], which is believed to function as a signalling scaffold for activating the innate immune pathway.

Although IFI16 was first described as a PRR for Herpes Simplex virus [57], it is now known to participate in sensing a broad range of microbial pathogens including HSV-1, CMV, HHV8, HIV, HPV, Francisella, and Listeria [17, 26, 52, 58-64]. We and others have characterized the mechanisms by which IFI16 senses HIV. In macrophages, IFI16 binds cytoplasmic HIV ssDNA and dsDNA through the HIN-200 domains, leading to activation of type I IFNs and other inflammatory cytokines through the canonical IFN pathway, which includes activation of the ER-bound adapter protein STING, the kinase TBK1, and transcription factor IRF3 [16, 17]. Removal of IFI16 from macrophages renders them more susceptible to HIV infection, supporting the role of this sensor in protecting these cells against infection [17].

While the HIN-200 domains of IFI16 are responsible for binding DNA, the PYRIN motif is involved in inflammasome formation [65, 66]. Inflammasomes are caspase-containing multiprotein complexes that play major roles in innate immunity and the production of the inflammatory cytokines IL-1β and IL-18. Interestingly, activation of IFI16 has been reported to drive inflammation in lymphoid CD4+ T cells infected with HIV [25, 26]. Upon infection of tonsillar T cells with HIV, 3-5% of the CD4+ T cells are productively infected with HIV

while up to 90% of them die in a manner that requires reverse transcription [25]. This HIV-induced cell death is caspase-1 driven and mediated by pyroptosis, and requires the expression of IFI16 [26]. Consistent results were recapitulated in a lamina propria aggregate culture model, where HIV-infected cultures had significantly fewer CD4+T cells and increased caspase-1 activation compared to mock treated cells [67]. More recently, it was demonstrated that IFI16-driven pyroptosis in tissue-derived T cells requires a synchronized and efficient form of viral transfer, which can be achieved by either cell-associated viral infection or spinoculation [68]. As such, although IFI16 can serve a protective role against HIV infection in macrophages, by initiating IFN secretion tissue-derived T cells, it may also promote pathogenesis by activating the highly inflammatory pyroptotic death pathway. Consistent with this, IFI16 expression positively correlates with markers of immune activation on CD4+T cells isolated from HIV treatment-naïve patients [69]. Clinical data from other diseases also support a role for IFI16 in driving restricted inflammation: IFI16 expression and secretion correlate with the severity of Sjögren's Syndrome [70, 71], and IFI16 expression is elevated in mucosal tissues from patients with active inflammatory bowel disease [72]. Because IFI16 is widely expressed in the cervix, placenta, ovary, fallopian tube, and endometrium [73], it is likely that IFI16 plays a role in sensing HIV as it attempts to establish infection in the FRT. Whether this manifests as limiting HIV replication in myeloid cells, or inducing pyroptotic CD4+ T cell death in this tissue, or some other process unique to the activity of IFI16 in the FRT, remains to be determined.

Cyclic GMP-AMP synthetase

cGAS is an interferon-stimulated gene that encodes a cytosolic protein of approximately 500 amino acids. cGAS can be found in a wide variety of cells including most lymphoid cells and myeloid cells. However, quiescent tonsillar CD4+ T cells do not express this protein [26], whereas activated blood-derived CD4+ T cells do [74]. cGAS contains an N-terminal domain with the ability to bind DNA, albeit rather weakly (binding affinity of >10uM), but not RNA [75]. Through this domain, cGAS can sense cytoplasmic synthetic DNA [76], mitochondrial DNA [77, 78], bacterial DNA [60, 64, 79-81], as well retroviral DNA [16, 18]. cGAS also contains a C-terminal (210-520aa) catalytic domain, consisting of an NTase and Mab21 domain, which upon activation induced by binding of DNA results in production of the small compound 2′5′-cGAMP (abbreviated cGAMP) from the cellular pool of ATP and GTP [82, 83]. cGAMP subsequently binds STING [84, 85], triggering its homodimerization and phosphorylation, which leads to activation of the TBK1/IRF3 pathway [86]. Recent studies indicate that the production of cGAMP and activation of STING is evolutionarily conserved, suggesting the importance of this pathway as a defence mechanism against foreign pathogens [87, 88].

cGAS is often considered the major sensor of HIV DNA in macrophages and DCs. Macrophages produce cGAMP in response to HIV infection in a manner that can be suppressed with reverse transcriptase inhibitors, suggesting that reverse transcribed intermediates of HIV are substrates for cGAS [16, 17]. Recently, it has been demonstrated that cGAS recognizes unique structured HIV ssDNA and that this recognition is dependent on flanked unpaired guanosines, which generate a Y-shaped DNA structure [89]. This mechanism is similar to the structural basis of how IFI16 recognizes the ssDNA stem-loop

structures of HIV DNA [17]. While evidence points to redundant functions of cGAS and IFI16 in macrophages [17, 60, 89], sensing in T cells is likely mediated by IFI16 [26, 74]. That being said, because recent studies demonstrated that cGAMP is capable of migrating between cells through gap junctions [82] and can be packaged into HIV particles and transferred to new target cells, including ones where cGAS is not expressed [90, 91], it is possible that cGAMP-mediated activation could be elicited in a variety of cell types, including T cells.

Whether cGAS is expressed in the FRT has not been established but since it is strongly expressed in macrophages and myeloid DCs, both residents of the FRT, it is plausible that this sensor will participate to the innate immune response against HIV transmission. Future studies are needed to determine whether cGAMP production in the FRT may lead to increased recognition and restriction of HIV during transmission.

Polyglutamine binding protein 1

A recent RNAi screen was recently carried out in primary human monocyte-derived DCs to identify candidate HIV sensors that work together with cGAS to drive the innate immune response [21]. This screen identified PQBP1, a nuclear protein associated with neurological disorders including Renpenning syndrome [92, 93]. Because phosphorylation of IRF3 and IKKε – processes involved in DNA-driven innate immune sensing – were both absent in PQBP1-deficient DCs upon HIV infection, it was concluded that expression of PQBP1 is important for sensing of HIV by DCs. Surprisingly, PQBP1 did not sense synthetic, mitochondria, or HSV DNA [21], suggesting that PQBP1 binds specific motifs unique to HIV reverse-transcriptase intermediates. As such, PQBP1 may, like cGAS [89] and IFI16 [17], recognize the stem-loop structures of HIV ssDNA. Although the DNA-binding domain of PQBP1 has been mapped to the N-terminal region, the structural basis of how this domain recognizes HIV but not other DNA viruses requires further studies.

Mechanistically, PQBP1 activity appears to be tightly coupled with that of cGAS, since depletion of PQBP1 decreased cGAMP production by DCs and macrophages. This may be due to a direct protein-protein interaction, since the N-terminal WW-domain of PQBP1 binds cGAS when both proteins are overexpressed in HEK293 cells [21]. All together, these data support a model where PQBP1 binds HIV DNA and directs it to cGAS. This in turn enables cGAS-mediated activation and cGAMP production. Of note, a similar mechanism has been suggested for how IFI16 activates cGAS [6, 62]. Further studies will be required to determine whether PQBP1, IFI16 and cGAS function redundantly or synergistically to regulate the innate immune response to DNA.

It should be pointed out that one consideration with the study that identified PQBP1 as an HIV sensor was the need to circumvent SAMHD1 restriction (through co-infection with vpx-containing VLPs) within the DC population prior to HIV infection. This was necessary to enable efficient HIV infection and reverse transcription, and promote innate immune sensing. Although investigating innate immune responses without boosting sensing of HIV PAMPs can be technically challenging [21], it is likely more reminiscent of what occurs *in*

vivo. Thus, future research should investigate how PQBP1 drives innate immune activation of HIV in the absence of vpx, for example in activated T cells.

HIV sensing in the FRT

In order to establish infection in the FRT, HIV needs to penetrate the squamous epithelium of the vagina or ectocervix, or the columnar epithelium of the endocervix or endometrium (see Figure 1). This penetration may be facilitated by mucosal disruption due to trauma or ulcerative sexual transmitted diseases. Within the interstitial space of the epithelium, passage of HIV across the epithelium may also be facilitated by the capture of virions by interdigitating cells such as Langerhans cells, macrophages or DCs [94-97]. After breaching the epithelium, HIV in the lamina propria can initiate infection of permissive cells including CD4+ T cells expressing the chemokine receptor CCR5 [98]. HIV may preferentially infect subsets of CD4+ T cells, including T-helper type 17 (Th17) cells, which are present in the FRT [99], and can additionally infect macrophages and DCs, in particular through cell-to-cell transfer [100, 101]. As described earlier, these cells express both TLRs and DNA sensors (cGAS, IFI16, and PQBP1), which should sense HIV and initiate an immune response to infection. How this sensing occurs will likely be affected by the unique properties of the FRT.

The FRT harbours a unique environment because this tissue needs to simultaneously tolerate sperm and the semi-allogeneic fetus while avoiding sexually transmitted microbial pathogens that can be detrimental for fertility. It achieves this by orchestrating a variety of immunomodulatory signals [102]. These immunomodulatory effects, however, may conceivably affect sensing of HIV and the development of an effective anti-HIV immune response. Although capable of providing a tolerant environment, the FRT at the same time is capable of producing an extensive array of inflammatory cytokines, some of which play roles in pregnancy establishment and protection against unwanted microbial pathogens [102]. Cytokines such as TNF-α are produced by the genital epithelium [103], and can increase permeability of primary polarized epithelial cells isolated from the FRT [104], which could facilitate translocation of HIV across the epithelial barrier and their ability to access cellular targets. Inflammatory cytokines such as IL-1, IL-1β, IL-2, IL15, TNF-α, and MCP-1 may also directly promote the ability of HIV to replicate in cellular targets [105-108]. Accordingly, having a general low level of inflammation in the FRT is associated with decreased risk of HIV transmission, likely by decreasing T cell activation and limiting recruitment of HIV permissive cells [109-112].

Because exposure of the FRT to seminal plasma (SP) is a common and physiological process, SP can in some sense be considered a component of the FRT environment. SP is the medium by which HIV enters the FRT and harbours a variety of bioactive factors whose physiological purpose is to promote reproductive success [113]. It provides a rich source of proinflammatory and immunomodulatory cytokines, such as TGF-β, IL-7, and IL-8, some of which can unfortunately promote HIV infection by upregulating HIV gene transcription or preventing CD4 T cell apoptosis [114, 115]. Of note, the levels of pro-inflammatory cytokines in SP differs between healthy individuals and HIV-infected patients, with acutely infected patients having higher levels of these cytokines as compared to chronic HIV and

uninfected donors [116]. These cytokines, together with other SP constituents, elicit a highly inflammatory response in cells of both the lower and upper FRT [103, 117-120]. This inflammatory response includes the secretion of chemokines, which can recruit HIV-permissive cells to the site of SP exposure [103, 121, 122] and increased NF-kB activation in cells which promotes HIV-LTR activity [116, 119]. The orchestrated physiological response of the FRT to SP exposure will likely affect sensing of HIV by affecting the types of target cells recruited to the site of exposure, and the ability of those cells to sense and limit replication of HIV. Since IFI16 and cGAS are both interferon inducible genes, it is possible that SP exposure initiates a positive feedback loop, where initial immune activation by SP increases expression and activation of HIV sensors, which upon detection of HIV are further activated. On top of this, because semen harbours amyloid fibrils that directly promote viral attachment to cellular targets [123-126], the efficiency of viral sensing may be augmented by virtue of SP's ability to increase access of PRRs to HIV PAMPs.

Hormones and sensing of HIV in the FRT

Due to the highly hormonally responsive nature of the FRT, studies on how HIV is sensed in the FRT need also to take into account the effects of the hormonal environment. The effect of hormones on HIV susceptibility has been studied extensively. Non-human primate studies have demonstrated that the secretory phase (when levels of progesterone are high) and the use of progesterone implants are associated with higher susceptibility to vaginal infection with SIV [127, 128]. In women, injectable progesterone-based hormones are potentially associated with higher rates of HIV infection, although there is no association between use of oral contraceptives and increased risk of HIV acquisition [129-133]. Progesterone-based hormones exert a multitude of effects on the FRT [134], and exactly which of these effects contribute most to HIV transmission risk is unclear.

The upper FRT, in particular the endometrium, is highly responsive to progesterone and undergoes a massive reorganization in a cyclical manner. Whether HIV transmission occurs across this tissue is unclear, but is conceivable given that peristaltic movements are known to direct luminal contents from the vagina into the upper FRT [135, 136], and that an SIV-based virus can ascend as high as the ovaries following intravaginal inoculation [137]. The relatively weak barrier of the single-layered columnar epithelium of the endometrium, along with recent data demonstrating the presence of HIV-permissive CD4+ T cells and macrophages in this tissue [138] further support the notion of the endometrium as a potential portal of entry for HIV. In addition, compared to the cervix, the endometrium is enriched in factors promoting HIV replication [139]. Nevertheless, how hormonally induced changes in the endometrium influence sensing of HIV is an underexplored area of research. Interestingly, however, recent studies in mice have demonstrated that expression of IFI16 homologs increased upon activation of the estrogen receptor [140-142]. In addition, in pigs increased levels of estrogen in the endometrium associate with increased expression of ISGs, including Interferon Regulatory Factors (IRFs) and the IFN-inducible antiviral protein Mx1 [143]. Studies with human macrophages revealed that by upregulating IFN, 17β-estradiol protects against HIV infection *in vitro* [144]. Together, these data suggest that innate sensing signalling pathways are regulated by female hormones and the efficiency of sensing of HIV in the FRT will likely be dependent on phase of the female menstrual cycle.

Finally, it should be mentioned that ovarian hormones also affect the lower FRT. Cyclical changes have been reported to occur in the vaginal epithelium of normal rhesus macaques [145]. Furthermore, in *ex vivo* studies using human cervical explants, only tissues obtained from women in their secretory phase sustained productive HIV replication, whereas non-productive infection was observed in tissues obtained from women in either their secretory or proliferative phase of the menstrual cycle or with an atrophic endometrium [146]. The mechanistic basis of this was attributed to non-productively infected tissues secreting higher levels of the CCR5 ligands CCL3 and CCL5, which might have curtailed HIV infection. By preventing entry of HIV into cellular targets, these cytokines would presumably also limit detection of HIV by the innate immune effectors, although this has yet to be directly demonstrated.

Conclusion

The FRT harbours T cells, macrophages, and DCs, which have been extensively characterized for their ability to sense and in some cases mount robust antiviral responses against HIV infection (Figure 1). Such *in vitro* systems, however, do not mimic the conditions under which HIV is sensed within the mucosal tissues. The FRT, in particular, is a unique site that is hormonally responsive and designed to be tolerant of semen components, while at the same time staying alert and limiting infection by undesirable microbial pathogens. Obtaining a more comprehensive understanding of how HIV is sensed at this portal of entry will require models incorporating mucosal components such as tissue-derived cells (including both permissive and non-permissive cells), genital secretions (SP and cervicovaginal fluid), and genital microflora. The simple question of whether sensing of HIV in the FRT benefits the virus or the host is not so simple to answer. The correct answer is likely context-dependent, and having *in vitro* systems that better mimic HIV transmission in the FRT, as well as incorporating the use of animal models, will help paint a more complete picture of the types of host response that averts infection and limits pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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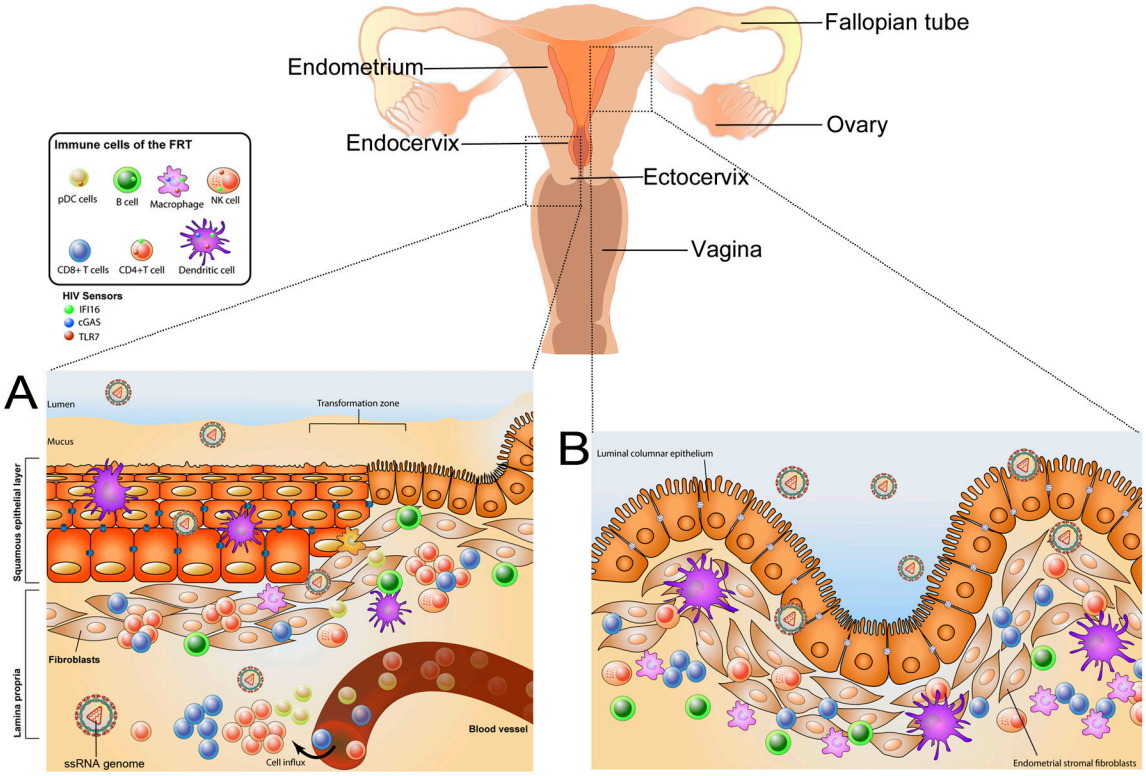

Figure 1.