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Published in:
Current opinion in virology

DOI:
10.1016/j.coviro.2017.01.001

Published: 01/01/2017

Document Version
Peer reviewed version

Citation for pulished version (APA):
Hertoghs, N., Geijtenbeek, T. B. H., & Ribeiro, C. M. S. (2017). Interplay between HIV-1 innate sensing and restriction in mucosal dendritic cells: balancing defense and viral transmission. *Current opinion in virology*, *22*, 112-119. https://doi.org/10.1016/j.coviro.2017.01.001

Interplay between HIV-1 innate sensing and restriction in mucosal dendritic cells: balancing defense and viral transmission

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Abstract

Innate sensing of HIV-1 by dendritic cells (DCs) initiates cell-intrinsic signalling programs that direct virus restriction and antiviral defences. These responses include the production of type I interferon (IFN) and a large number of IFN-stimulated genes (ISGs) with a broad spectrum of antiviral effector functions. Initial interactions of HIV-1 at the mucosal surfaces with DC-expressed innate immune factors including cGAS, TRIM5α and SAMHD1 are predictive of viraemia, inflammation and disease pathogenesis. Here, we review the molecular basis of HIV-1 sensing in the two major mucosal DC subsets, i.e. epithelial Langerhans cells and subepithelial CD11c+ conventional DCs. We discuss the concerted actions of the host restriction factors and innate sensors as well as viral evasion mechanisms in determining HIV-1 susceptibility to infection and directing antiviral adaptive immune responses.

Introduction

Innate antiviral defence is crucial for halting initial HIV-1 infection and dissemination, whereas adaptive immune responses are vital for elimination of virus-infected cells and long-term protection. Recent studies suggest that the initial events and the inflammatory profile during acute retroviral exposure across mucosal surfaces are predictive of the viral load set point and the rate of disease progression. Early inhibition of type I IFN responses by blocking the IFNα/β receptor in SIV-infected rhesus macaques results in increased SIV viraemia and accelerated CD4 T-cell depletion, suggesting that type I IFN responses direct anti-HIV-1 responses [1]. However, high levels of the ISG IP-10 (interferon gamma-induced protein 10) and the cytokine TNF-α (tumor necrosis factor α) in the plasma during primary HIV-1 infection in humans are associated with poor viral control and rapid disease progression [2,3]. Thus, a tight regulation of the induction of inflammatory responses during HIV-1 infection is required to mount an effective early antiviral responses without deleterious effects. Remarkably, recent research in elite controllers, a subgroup of HIV-1-infected individuals able to control viral replication in the absence of antiretroviral therapy, underscores the *in vivo* relevance of dendritic cells (DCs) where it was shown that DC maturation and secretion of type I IFN rapidly after HIV-1 infection induces protective HIV-1 specific CD8+ cytotoxic T cells [4]. In this review, we will focus on the innate intrinsic responses by mucosal DC subsets during primary HIV-1 infection and how components of the type I IFN system including innate sensors and restriction factors determine cell-intrinsic resistance to infection. Furthermore, we will discuss the implications of the interplay of these host effectors on DC activation and DC-mediated viral transmission.

Many branches of DC functions at the crossroads of primary HIV-1 infection

Among the different cellular components of mucosal immunity, DCs play a central role in orchestrating innate and adaptive T-cell mediated immune responses [5]. DCs are professional antigen-presenting cells, which reside in the mucosa (including vagina, foreskin, mouth and colorectal mucosal) and thereby proposed to be one of the first immune target cells to detect HIV-1 during sexual transmission [6–9]. Equipped with pattern-recognition receptors (PRRs), DCs sense viral pathogen-associated molecular patterns (PAMPs). Triggering of PRRs results in the production of Type I IFN and IFN-stimulated genes (ISGs) to control virus spread as well pro-inflammatory cytokines and chemokines necessary to recruit other immune cells and to initiate adaptive T-cell-mediated immune responses [10]. PRRs mediate internalization and processing of pathogen-derived antigens for subsequent

antigen presentation to naïve T cells in the context of MHC molecules [11]. Optimal priming of naïve T cells into effector antiviral T cells depends on the maturation status of DCs, i.e., a cascade of phenotypical changes in DCs and secretion of DC-derived soluble mediators [5]. A hallmark of DC maturation is the upregulation of MHC-I/II, co-stimulatory molecules CD80, CD86, CD70 and lymphoid tissue homing receptor CCR7. DC-mediated cytokine production including IL-12 and IL-27 are required to evoke CD4+ TH1 responses and CD8+ cytotoxic T cell response, respectively, to clear virus-infected cells and mount a memory T-cell-mediated immune response [12]. For the establishment of HIV-1 infection, the virus has to spread from the mucosal entry sites to the CD4+ T cell-enriched areas in the lymphoid tissues. The ability of DCs to migrate from the periphery to lymph nodes supports also an important role for DCs not only in HIV-1 specific adaptive immune responses, but also in viral transmission and disease progression.

Cell-intrinsic antiviral responses during mucosal HIV-1transmission

Two major DC subsets reside in human mucosal tissues, which can be distinguished by their specific location within mucosal surfaces as well as phenotypical and functional characteristics [13]. Langerhans cells (LCs) reside at mucosal epithelia and express C-type lectin receptor (CLR) langerin whereas myeloid CD11c+ conventional DCs (myDCs) located at the subepithelia are characterized by the expression of the CLR DC-SIGN[14–16]. It has been suggested that myDCs are not productively infected by HIV-1 [17,18]. However, several other studies have shown that monocyte-derived DCs, an experimental model for myDCs, are efficiently infected by HIV-1 [19–22]. myDCs express PRRs that sense HIV-1 but HIV-1 hijacks their signalling for replication as engagement of HIV-1 by the PRRs DC-SIGN and TLR8 promotes viral replication in myDCs [23]. Infected DCs act as virus producers that promote transmission of *de novo* HIV-1 particles to target T cells [24,25]. In addition, myDCs can transmit virus without the need for productive infection; DC-SIGN on myDCs acts as a *trans* receptor that binds to HIV-1 and transmits the virus to neighbouring target cells [15,26]. Strikingly, HIV-1 infected DCs do not undergo maturation and therefore have a diminished capacity to activate naïve T cells [18,19,22]. Furthermore, DCs are unable to produce type I and III interferon in response to HIV-1 [27,28]. The lack of DC maturation and type I IFN production, which are prerequisites for an effective antiviral immune response, might be due to either a lack of sensing by DC-expressed PRRs or the result of evasion mechanisms of the virus on PRR-induced antiviral signalling programs.

In contrast, primary immature LCs do not become infected and act as a natural barrier against HIV-1; LCs restrict HIV-1 infection [14,29–31]. LCs efficiently bind and internalize HIV-1 via langerin. However, capture of HIV-1 via langerin does neither allow infection nor transmission but rather sequesters the virus into Birbeck granules [14,29,30]. These LC-specific organelles have a superior ability in viral degradation and contribute to the intrinsic antiviral function of langerin resulting in a post-entry restriction of HIV-1 infection in LCs [14,30,32]. Little is known about the innate sensing of HIV-1 in LCs and whether these cells become activated or produce type I IFN upon HIV-1 exposure[31].

The different roles of mucosal DCs on primary HIV-1 infection and viral transmission might represent a functional specialization of LCs and myDCs on antiviral responses or the result of the concerted action of innate sensors and restriction factors. Deciphering the molecular basis underlying the LC-intrinsic restriction mechanism and defective sensing in myDCs might provide rationale for novel strategies to provide both viral restriction and innate sensing by mucosal DCs and thus, mount a protective antiviral immune response early upon mucosal HIV-1 transmission.

HIV-1 sensing and restriction in DCs: components of the IFN-I system

Initially it was suggested that HIV-1 escapes immunosurveillance by not efficiently infecting DCs. Therefore, restriction of HIV-1 by these cells minimizes the capacity to mount a sufficient innate immune response, as cytosolic sensors are not triggered by HIV-1 DNA products. In 2013, cyclic GMP-AMP syntase (cGAS) was identified as the cytosolic DNA sensor that is triggered by HIV-1. In short, Polyglutamine binding protein 1 (PQBP1) binds to reverse transcribed cDNA, and mediates the interaction with, and activation of cGAS [33]. Upon sensing of cDNA in the cytosol, cGAS synthesizes cyclic GMP-AMP (cGAMP) which binds and triggers the adapter molecule STING, which activates the transcription factor IRF3 via TBK-1, leading to IFN-I production [34–36].

Type I IFN binding to cell surface IFNα/β receptor in an autocrine and paracrine manner and subsequent downstream signalling JAK/STAT cascade activation results in the induction of an array of ISGs, which enhances the cell-intrinsic resistance to infection. Among the ISG-encoded proteins are the so-called host restriction factors that have been shown to directly supress retroviral replication and dissemination, such as TRIM5α (tripartite motif-containing protein 5α), SAMHD1 (SAM-and HD domain-containing protein 1), APOBEC3 (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3), Mx2 (Myxovirus resistance 2), tetherin and more recently IFITM (Interferon-induced transmembrane proteins)

and SLFN11 (Schlafen 11). The mechanisms of suppression of each of the restriction factors have been reviewed in detail elsewhere [37,38] and here we will focus on the antiviral effector functions of TRIM5a and SAMHD1 in HIV-1 infected DCs.

TRIM5α is an E3-ubiquitin ligase that suppresses retroviral replication early after viral fusion by targeting incoming viral capsid for degradation, which interferes with reverse-transcription processes [39–41]. Both proteosomal and autophagic-dependent TRIM5α mechanisms have been proposed to mediate HIV-1 capsid degradation [42,43]. In addition, TRIM5α can also act as a PRR and trigger innate TAK-1 and NF-kB-dependent signaling pathways [44]. Furthermore, rhesus TRIM5α–mediated heightened capsid-specific CD8+ T cell activation suggests that TRIM5α couples restriction to adaptive cellular immune responses [45]. Notably, non-human primate DCs lack TRIM5α-mediated restriction, while still operative in other primary cell targets (macrophages and CD4+ T cells) [46,47]. Subcellular localization and the small ubiquitin-related modifier (SUMO) modification account for the lack of retroviral restriction [47–50]. DeSUMOylated TRIM5α in DCs accumulates in the nucleus, which correlated with the lack of retroviral restriction and thus TRIM5α nuclear sequestration allows innate sensing of viral DNA by cGAS in DCs and subsequent type I interferon production [47]. The current TRIM5α restriction paradigm comprises that rhesus and other simian TRIM5α proteins, but not human TRIM5α, bind HIV-1 capsid and thereby efficiently block HIV-1 infection [51–55]. The findings that genetic variation in *trim5α* genes are associated with differential clinical course of infection and that some primary HIV-1 isolates are 8-fold more sensitive to human TRIM5α restriction than HIV-1 lab-adapted strains suggest that TRIM5α antiviral activity may be underestimated in humans [56,57].

The restriction factor SAMHD1, is highly expressed in myeloid cells like DCs and macrophages and has been shown to limit HIV-1 cDNA synthesis in myDCs [58–61]. Both dNTPase and RNAse activities of SAMHD1 have been implicated in the SAMHD1-mediated HIV-1 restriction in myDCs, resulting in limited reverse transcription processes [59,61]. Interestingly, LC infection is restricted after viral fusion, but in contrast to myDCs, this post-entry restriction mechanism is independent of SAMHD1 antiviral activity [30,32]. Thus, differences in antiviral activity of SAMHD1 between LCs and myDCs not only suggest that SAMHD1 is a cell-specific restriction factor, but also strongly suggest that specific cell-intrinsic antiviral signature programs are initiated at the mucosal sites, which can determine the net outcome of HIV-1 infection and antiviral immunity.

The observed restriction by SAMHD1 in myDCs has been suggested to lead to a diminished induction of innate immunity, since active replication of HIV-1 is needed to activate the cGAS sensing mechanism. However, several studies do not support this model, as productive infection of DCs does not lead to activation and type I IFN responses, even when infection was enhanced by degradation of SAMHD1 [19,22,62]. Part of these differences might be due to use of different viruses as many studies use VSV-G pseudotyped HIV-1 [18], which triggers different receptors than HIV-1 [23]. Taken into account that the signalling via DC-SIGN and TLR8 leads to a favourable outcome for the virus illustrates that the mode of entry has an effect on infection and activation [23]. However, infection alone might also not enough for the induction of type I IFN responses as HIV-1 similar to other viruses might actively inhibit sensors via different mechanisms [63]. In recent years, several studies have aimed at identifying a putative sensor for HIV-1 in DCs. DCs are known not the be strongly reactive against HIV-1 even though several PRRs sense HIV-1, like TLR8 and DC-SIGN. This however, does not lead to a strong antiviral state, but rather induces and support transcription of the HIV-1 proviral genome [23]. Several studies have shown that DCs are capable of sensing HIV-1, but that there are many mechanisms that HIV-1 employs to escape immunosurveillance, often involving host factors that shield HIV-1 PAMPs. An interesting factor is TREX1 that eliminates reverse transcriptase-synthesized DNA products, thereby preventing triggering of cGAS and blocking TREX1 leads to a robust IFN production by DCs upon HIV-1 infection via cGAS [64].

Taken together, there are two separate ways of preventing immune activation by HIV-1; by preventing sensing in the cytosol, or by preventing infection at all. Which of the mechanisms is deemed the most crucial probably depends on differences in experimental models. Therefore, it is preferable to confirm experimental findings with models that accurately resemble the *in vivo* situation such as primary DC subsets isolated from tissues. Investigating the sensor mechanisms in primary DCs instead of cell-lines will resolve some of the controversial questions.

Apart from the production of newly synthesized cDNA, the replication cycle of HIV-1 delivers several potential targets for cytosolic sensors. The ssRNA that enters the cytosol upon HIV-1 infection is not immunogenic, as these RNA strands are Poly-A-tailed and capped, similar to host mRNA molecules [65]. However, a study suggests that the triggering of RIG-I-like receptors (RLR) is prevented by SKIV2L, a host exonuclease that degrades and thereby shields incoming viral ssRNA [66]. Additionally, Cofactors cleavage and

polyadenylation specificity factor subunit 6 (CPSF6) and cyclophilins Nup358 and CypA are essential in preventing IFN production in macrophages [67].

Taken together, these studies show that HIV-1 employs many mechanisms via host factors to shield its PAMPs from the host immunosurveillance. The level and timing of IFN-I early upon retroviral have important consequences in viral transmission and disease progression.

Dendritic cells mediate viral transmission: role for mucosal inflammation and type I IFN production

The early innate immune response that is elicited by invading viruses during HIV-1 transmission is insufficient to protect against the invading virus. Many studies have shown that DCs contribute to HIV-1 transmission. There are several studies describing infection of DCs, but the general paradigm states that DCs bind HIV-1 but do not become infected themselves, and are therefore unable to sense the virus. As a Trojan horse, DCs transport HIV-1 to the lymph node where it transmits the virus to CD4 T-cells [15].

As mentioned before, LCs are not susceptible to HIV-1 infection, and the interaction with langerin leads to capture and degradation of the virus [14]. However, during co-infections with other pathogens, in the case of an STI for instance, restriction in LCs is abrogated, presumably because activation of LCs leads to downregulation of langerin, which renders the cells more susceptible to HIV-1 infection [14,29,68]. Thus, DC subsets and inflammation affect HIV-1 susceptibility during sexual transmission and it has been suggested that only viruses with specific attributes allowing them to overcome these barriers establish infection of the host.

Recently, methods have been devised to study the phenotype of HIV-1 just after transmission, as this can give insight into the factors contributing to successful transmission of HIV. In most of the cases, CCR5 using strains (R5) are transmitted, irrespective to the presence of CXCR4 (X4) using strains in the transmission fluid. Many studies have been devoted to unravel the mechanism behind this selection [69]. Recently, it has been shown that LCs exhibit a selective preference for transmitting R5 strains, even though both X4 and R5 using strains were able to infect primary LCs, but only R5 strains were transmitted to target cells in vitro [29]. This study underscores that specific mechanisms exist that limit X4 virus transmission. Other studies suggest that target cells *in situ* do not express CXCR4 to the same level as CCR5, although conflicting findings have been published [29]. Furthermore, the R5 selection occurs in all transmission routes, also via blood, suggesting that a single cell type is not the sole determinant of the R5 selection. Thus, detailed studies on the mechanisms of R5

selection will allow us to not only understand the important selection mechanisms but also to devise new strategies to prevent R5 transmission.

Indeed, recent studies have revealed specific characteristics for transmitted viruses, by investigating the transmitted viruses in depth, by employing a new technique called single genome sequencing (SGA) [70]. Here, limiting dilutions of cDNA are serially diluted in which each sample contains only one template of an HIV-variant from the plasma of an acutely infected individual. After amplification, each virus type is sequenced. This enables the thorough characterization of the transmitted viruses before seroconversion [70]. These studies have led to the understanding that in 60-90% of the transmission events, only one or a few HIV-1 variants are transmitted [71]. Taken into account that transmission fluids like semen or cervicovaginal fluid contain many HIV-1 variants, these so-called transmitted founder viruses (T/F virus) might harbor subtle differences that render them more successful in escaping the restrictions during transmission. Information about these T/F viruses gives vital clues about the decisive and critical events during transmission. Several studies have shown that T/F viruses are less prone to IFN restriction compared to chronic viruses [72,73]. This suggests that somewhere in the course of transmission, IFN is produced. The relative resistance would give a crucial advantage that leads to transmission to the new host.

Further investigations have indicated that the T/F virus phenotype harbors an Env protein that has less N-linked glycosylation sites [72]. This finding is remarkable, as HIV-1 is known to shield its Env protein with glycans in order to escape the recognition of neutralizing antibodies. Lacking specific glycosylation sites might make the virus less susceptible to certain factors in the cervicovaginal fluids, as has been suggested before. Another explanation is that lesser glycosylation sites decreases the interaction probability with CLRs on local immune cells such as DCs and LCs. Another study found that the amount of Env seemed to be increased on T/F viruses, which increased the binding and transmission by DCs [72,74]. Moreover, T/F viruses have been shown to be more infectious, and replicate better in T-cells, they are captured more efficiently by DCs and transmitted to T-cells [72]. These studies are important to understand the innate responses encountered by HIV-1 during transmission and further research will undoubtedly uncover more of these mechanisms.

Conclusions and outlook

DCs are crucial in the induction of both innate and adaptive responses to HIV-1 but paradoxically these cells are also responsible for viral transmission. The balance between antiviral immunity and viral transmission determines HIV-1 susceptibility and pathogenesis.

In recent years it has become clear that host restriction factors and sensing mechanisms control the function of DC subsets in HIV-1 infection and pathogenesis. The importance of type I IFN-mediated responses in blocking viral replication within the cell but also in promoting adaptive immunity to HIV-1 underscores the importance of innate sensing in mucosal DC subsets. The more so, since HIV-1 viruses that establish HIV-1 infection in the host, T/F viruses, are less sensitive to type I IFN.

Thus, our knowledge about intrinsic restriction and sensing mechanisms improved greatly in recent years, but many important details of the spatio-temporal triggering of these host antiviral factors and how they act in concert within primary human DC subsets using clinically-relevant HIV-1 strains remains poorly defined. Understanding these crosstalk mechanisms should ultimately provide novel therapeutic targets to selectively limit viral transmission while preserving innate immune recognition. In addition, there is accumulating evidence that components of the type I IFN response, such as TRIM5α can trigger autophagy as well as components of autophagy machinery can limit cGAS-mediated type I IFN production [43,75,76]. Harnessing this intracellular degradative process may potentiate innate sensing as well as aid the design of novel small-molecule inhibitors that can act as antivirals.

Furthermore, uncovering viral immune evasion mechanisms employed by HIV-1 as well as defining novel viral sensors is paramount to design novel strategies to antagonize aberrant activation of PRRs or block interaction between viral PAMPs and host effector molecules. Deciphering the molecular mechanisms by which genetic mutations in these host factors are associated with disease pathogenesis or inflammatory/autoimmune diseases may provide novel insights to boost immunogenicity of vaccines and antivirals as well as mitigate unwanted inflammation.

Acknowledgements

This work was supported by the Dutch Scientific Organization NWO (VENI 863.13.025), Aids Fonds (2012042) and European Research Council Advanced grant (670424).

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Of special/outstanding interest:

- Sandler, *Nature* 2014.

(**) Crucial data on in vivo role of type I IFN production on SIV viraemia and disease progression

This paper shows that IFN-I helps to decrease the SIV reservoir size and accelerated CD4 T-cell depletion with progression to AIDS, while administration of IFN induced a worse prognosis.

- Martin-gayo, *Plos pathogens* 2014

(**) Here the authors show that DCs from Elite controllers are better able to produce IFN-I and to activate CD8 T- cells. This effect was associated with decreased activity of SAMHD1 and LEDGF/p75. It underscores the *in vivo* relevance of DC function on HIV-1 pathogenesis and disease progression.

- Portilho, *Cell reports* 2016

(*) TRIM5a nuclear sequestration allows DC sensing of retroviral DNA by cGAS. The findings show that rhesus TRIM5a restriction is cell specific. Primate DCs lack TRIM5a restriction, in contrast to other target cells, like macrophages and T-cells

- Czubala, *Journal of Investigative Dermatology* 2016: SAMHD1-independent post-entry restriction in Langerhans cells

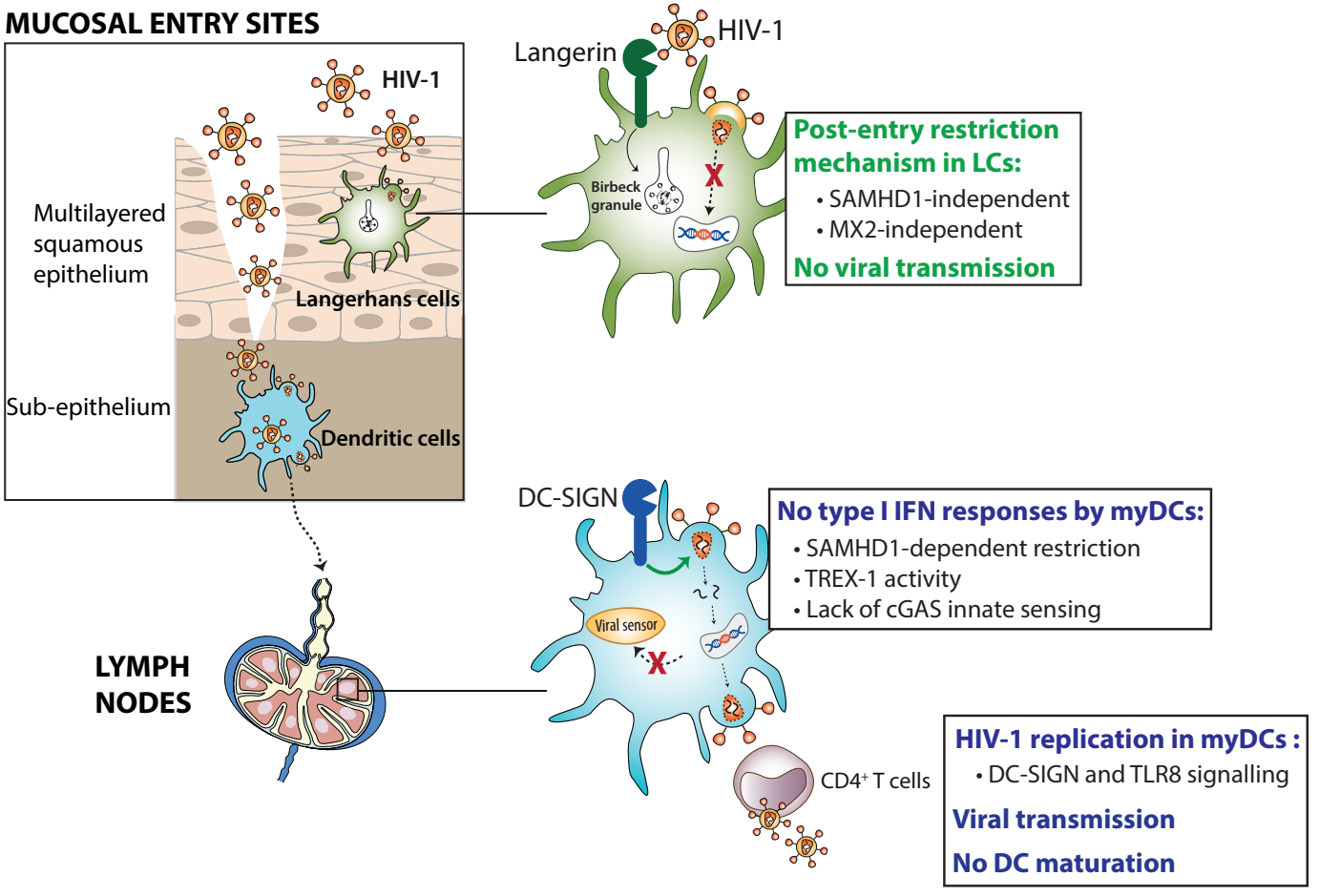
(*) The authors show that restriction in LCs is not dependent on SAMHD1 nor MX2, but another factor post-fusion restriction factor

- Gao, *Science* 2013

(*) The authors identify cGAS as a cytosolic sensor of HIV-1 cDNA

- Parrish, *Proceedings of the National Academy of Sciences of the United States of America* 2013

(**) The authors use SGA, which is a very ingeneous method to study the phenotypical properties of T/F viruses and find that these viruses are more resistant to IFN, have higher Env content, and are more infectious than chronis controls


MUCOSAL ENTRY SITES
HIV-1
Multilayered squamous epithelium
Langerhans cells
Sub-epithelium
Dendritic cells
LYMPH NODES
Langerin
HIV-1
Birbeck granule
X
Post-entry restriction mechanism in LCs:
• SAMHD1-independent
• MX2-independent
No viral transmission
DC-SIGN
Viral sensor
X
No type I IFN responses by myDCs:
• SAMHD1-dependent restriction
• TREX-1 activity
• Lack of cGAS innate sensing
CD4+ T cells
HIV-1 replication in myDCs :
• DC-SIGN and TLR8 signalling
Viral transmission
No DC maturation