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Viral and cellular mechanisms of the innate immune sensing of HIV

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HIV-1 replicates in immune cells that normally respond to incoming viruses and induce antiviral immune responses. Under this constant surveillance, how HIV-1 interacts with the host to escape immune control and causes immunopathology is still being untangled. Recently, a series of HIV-1 interactions with innate sensors of viruses expressed by immune target cells have been identified. Here, we review the HIV-1 factors that escape, engage and regulate these innate immune sensors. We discuss the general principles of these interactions as well as the remarkable cell-type specificity of the regulatory mechanisms and their resulting immune responses. Innate sensors directly intersect viral replication with immunity, and understanding their triggering, or lack thereof, improves our ability to design immune interventions.

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Introduction

While HIV-1 induces an immune response in the infected host, this response is unable to sterilize infection and generally poor at controlling viral replication, leading to AIDS. The tropism for HIV-1 to immune cells suggests that viral replication in the immune system disables it, which leads to AIDS-induced pathogenesis [1]. However, how HIV-1 escapes protective immunity in a host that is initially immunocompetent is still unresolved. Furthermore, what are the processes of viral replication that lead to immunodeficiency remains a disputed question. In the recent year, the identification of HIV-1 interactions with the innate immune system has provided fresh views on these two important problems. At the core of the innate immune system are innate immune sensing pathways, which consist of non-clonal processes that relay changes in host state to immunity. In the context of HIV-1, these changes can be directly induced by the virus, as well as indirectly through tissue damages and disruptions of cellular integrity, for example. Here, we will review the main implications of HIV-1 proteins and nucleic acids in innate immune sensing and the underlying cellular and molecular mechanisms.

Viral nucleic acids

Sensing of viral nucleic acids by TLRs

The HIV viral particles contain two copies of the viral genome as ssRNA. TLRs constitute the first line of sensors encountered by HIV in the form of exogenous viral particles. Among all TLRs, TLR7 and TLR8 have the capacity to recognize the genomic ssRNA of HIV [2•] (Table 1). Recognition of the HIV-1 ssRNA has been best analyzed in plasmacytoid dendritic cells (pDCs) thanks to the rapid and strong production of type I interferon that ensues [3•]. In pDCs, recognition is mediated by TLR7 [4], occurs in an endosomal compartment [5,6], does not require productive viral replication [6] and leads to the production of IFNα and TNFα [5]. Recognition of the HIV-1 RNA by TLR7 and TLR8 has also been observed in monocytes and monocyte-derived dendritic cells (MDDCs). In monocytes, it has been shown that recognition of the HIV-1-derived ssRNA by TLR7 and TLR8 leads to production of IL6 and TNFα in one study [7], while infection of monocytes by HIV-1 was proposed to induce inflammasome activation but not production of IFNs in other studies [8,9]. In MDDCs, in contrast, it has been proposed that recognition of the HIV-1 RNA by TLR7 and TLR8 signals to increase subsequent viral transcription and hence viral production by the cells and no immune response was reported [10]. Finally, it was recently proposed that TLR7 expression in CD4+ T cells is functional for recognition of the HIV-1 RNA [11]. The outcome is complex as it induces simultaneously anergy of the T cells and an increase in viral production. The viral particles contain also additional nucleic acids, such as the cell-derived tRNA used for priming reverse transcription, and there putative recognition by TLRs remains an intriguing possibility. Overall, the viral genome in viral particles has clearly emerged as an important viral nucleic acid for TLR activation.

After viral fusion with the cell, HIV-1 particles release their capsid in the cytosol, which contains the viral ssRNA. It is reverse transcribed in viral cDNA, which is transported to the nuclear genome for integration. During these processes, the virus-derived nucleic acids that are generated are putative triggers for innate immune

Table 1

Viral factors in HIV-1 that are directly recognized by innate sensors

Viral factor	Innate sensor	Innate immune response to the viral component	Refs
ssRNA in the particle	TLR7 in pDCs	Type I IFN	[2•,3•,5]
	TLR7 and TLR8 in monocytes	IL1β, IL6 and TNFα	[7–9]
Viral dsDNA and related RT products	cGAS recognition in MDDCs	Type I IFN and activation of antigen presentation when SAMHD1 is abrogated	[20••,21••]
	Unknown sensor in MDMs	Type I IFN when CypA or CPSF6 are inhibited	[22•]
	cGAS in TREX1-deficient MDMs	Type I IFN when TREX1 is absent	[14•,20••]
	IFI16 in tonsilar CD4+ T cells recognition	IL1β and pyroptosis; type I IFN	[16••,23,64]
	Unknown sensor in SLX4-inhibited cell lines	Type I IFN	[15••]
Membrane-tethered viral particles	Tetherin	Inflammatory cytokines production	[42••,43]

sensors. These include potentially a wide range of nucleic acid species: dsDNA, structured ssRNA, short ssDNA, linear ssRNA, hybrids RNA:DNA and degradation or modified products. In the past years, a series of studies have described that HIV-derived DNA species can activate cytosolic innate sensors [12••,13,14•,15••,16••] (Table 1).

Sensing of cytosolic viral nucleic acids in dendritic cells

In MDDCs, HIV-1 infection does not normally induce an innate immune response (Figure 1a) [12••,17]. Bypassing the SAMHD1 restriction [18••,19••] upon infection with the viral Vpx protein (see below for the role of Vpx) leads to production of type I interferon and innate immune activation (Figure 1b). Accordingly, HIV-2, which naturally encodes Vpx, also induces this response. In HIV-2, it requires the presence of the viral cDNA in the cytosol, but does not require nuclear entry of the genome and viral integration (Figure 1c). In HIV-1, activation further requires integration and expression of newly synthesized capsid [12••] (see below for the role of capsid) (Figure 1b). In both cases, the DNA sensor cyclic GMP–AMP synthase (cGAS) is required, a sensor that produces the second messenger cyclic GMP–AMP (cGAMP) [20••,21••]. cGAMP has a high affinity for STING, an ER-resident protein, and its binding to STING induces the recruitment of a signaling machinery that ultimately leads to activation of IRF3. The requirement for cGAS indicates that the cytosolic viral cDNA is required for sensing in the case of HIV-1, even if the incoming viral capsid is not permissive. Overall, the viral cDNA is thus essential for innate sensing of the virus, but it is constrained by the viral capsid context: depending on its amino acid sequence and interaction with cofactors (see below), the viral capsid has the ability to either shield the viral cDNA away from innate sensors or favor the viral cDNA access to sensors.

HIV-1 can replicate to some extent in DCs when SAMHD1 is active (in the absence of Vpx) leading to a significant fraction of infected cells. However, this does not trigger an innate immune response and sensing requires alleviation of SAMHD1 restriction [12••]. Even with Vpx, it is not necessarily all the infected cells at a given rate of infection that trigger an innate immune response [12••]. Here, it should be noted that SAMHD1 impacts the efficiency of reverse transcription in the cytosol and that the frequency of infected cells (as indicated by viral or reporter protein expression) does not necessarily reflect the total amount of viral cDNA in the cytosol. At a given frequency of infected cells, it is likely that cells without SAMHD1 contain a much larger pool of cytosolic cDNA sufficient to activate cGAS, whereas in the presence of SAMHD1, the quantity of cytosolic viral cDNA produced does not reach a sufficient threshold to trigger cGAS. The relative abundance of these cytosolic pools may not necessarily relate to the infection rate of the cell. Indeed, it is very likely that several steps after reverse transcription are saturable and/or that not all RT products are competent for transport to the nucleus and integration. When considering these innate immune sensing pathways, it is essential to consider the relevant viral material (e.g. the amount of cytosolic viral cDNA and the capsid), and not only the apparent infection rate of the cells.

Sensing of cytosolic viral nucleic acids in CD4+ T cells and macrophages

In monocyte-derived macrophages (MDMs) and CD4+ lymphocytes, HIV-1 infection proceeds and does not normally induce detectable type I interferon production [14•,22•] (Figure 1d). However, in the absence of TREX1, a DNA exonuclease, HIV-1 infection induces a type I interferon response [14•]. It is thought that TREX1 normally degrades by-products of the viral reverse transcription process, and these products accumulate in the absence of TREX1, leading to innate sensor activation. The response in TREX1-deficient cells requires the DNA sensor cGAS [20••] as well as STING, TBK1 and IRF3. In addition to TREX1-deficient cells,