Review

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Inflammasomes in Human Immunodeficiency Virus Type 1 Infection

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Abstract

Innate immune responses are the host's first line of defense against human immunodeficiency virus type 1 (HIV-1) infection, with pattern recognition receptors detecting viral specific pathogen-associated molecular patterns and initiating antiviral responses. In response to HIV-1 nucleic acids or proteins, some pattern recognition receptors have the ability to assemble a large multiprotein complex called the inflammasome, which triggers pro-inflammatory cytokine release and a form of lytic programmed cell death called pyroptosis. Here, we review our current understanding of the mechanism of the inflammasome in sensing HIV-1 infection. Furthermore, we discuss the contribution of inflammasome activation in HIV-1 pathogenesis as well as potential strategies of targeting inflammasome activation for the treatment of HIV-1 infection.

Keywords: HIV-1; Inflammasomes; CARD8 protein; Pyroptosis

Introduction

The innate immune system uses germline-encoded pattern recognition receptors that detect distinct conserved microbial structures or activities to defend against infection.[1,2] A set of pattern recognition receptors initiates the assembly of a multiprotein signaling complex called the inflammasome. After detection of microbial products or cytosolic danger signals, most canonical inflammasome sensors oligomerize and recruit an adaptor protein called apoptosis-associated speck-like protein containing CARD (ASC). This results in the formation of inflammasome specks, within which ASC recruits and activates the inflammatory caspase-1. Subsequently, active caspase-1 promotes processing and secretion of pro-inflammatory cytokines interleukin (IL)-1β and IL-18. Active caspase-1 also cleaves gasdermin D, leading to pyroptosis, a type of programmed cell death.[3,4]

Several inflammasome sensors have been directly or indirectly implicated in the response to human immunodeficiency virus type 1 (HIV-1) infection, such as NOD-like receptor (NLR) family pyrin domain-containing 3 (NLRP3), interferon inducible protein 16 (IFI16), and caspase recruitment domain family member 8 (CARD8).[5–7] However, the specific contribution of each inflammasome to HIV-1 pathogenesis and treatment is still poorly understood. In this review, we summarize potential mechanisms of inflammasome activation during the course of HIV-1 infection. Furthermore, we discuss the critical role of inflammasome activation in HIV-1 pathogenesis and its therapeutic implications.

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Inflammasome sensing of HIV-1

$CD4^+$ T cell loss during chronic HIV-1 infection is a hallmark of acquired immunodeficiency syndrome (AIDS) progression. The molecular mechanisms of $CD4^+$ T cell depletion during HIV-1 infection are not fully understood. It is generally believed that chronic immune activation, rather than viral protein cytotoxicity, causes $CD4^+$ T cell loss and HIV-1 pathogenesis.[8–10] Moreover, several species of African nonhuman primates do not experience $CD4^+$ T cell depletion despite chronic infection with simian immunodeficiency viruses (SIVs) and high levels of viral replication. One explanation for the resistance of natural SIV hosts to SIV-associated $CD4^+$ T cell loss may be that they do not develop features of chronic immune activation.[11–13] However, the mechanisms through which chronic immune activation may be linked to $CD4^+$ T cell depletion have not been elucidated. Notably, one study showed that abortive HIV infection triggers pyroptosis of resting $CD4^+$ T cells, contributing to HIV-1 pathogenesis by depletion of most $CD4^+$ T cells.[14] Inflammasome activation also leads to the release of certain cytokines that may contribute to chronic immune activation,[15,16] although whether this plays a role in the progression to AIDS remains to be determined. Furthermore, what role the inflammasome plays in adaptive immune responses during HIV-1 infection warrants further study.

Recent studies have identified cytosolic inflammasome sensors that recognize nucleic acids and protein components associated with or generated from HIV-1 infection. The inflammasome sensors currently known to be involved in HIV-1 infection include NLRP3, IFI16, CARD8, and other inflammasomes [Table 1, Figure 1].

Sensing of HIV-1 through NLRP3

NLRP3 is one of the most broadly studied inflammasome sensors and has the potential to sense a diverse set of ligands. The NLRP3 inflammasome may be activated by various stimuli including cytosolic K^+ efflux, cytosolic Ca^{2+} influx, or mitochondrial reactive oxygen species (ROS).[33] NLRP3 inflammasome activation results in caspase-1–dependent IL-1β and IL-18 secretion, as well as gasdermin D–mediated pyroptosis [Figure 1].[3,33,34]

Table 1: Inflammasome sensor for HIV-1

Sensor	Ligand (activator)	Cell type	Refs
NLRP3	HIV-1 RNA, ROS	PBMC	17
NLRP3	HIV-1 RNA, ROS	PBMC, DCs	18
NLRP3	HIV-1 RNA, ROS	Microglia, MDM	19,20
NLRP3	HIV-1 Vpu, K^+ efflux	MDM	21
NLRP3	HIV-1 gp120	Microglia	22,23
NLRP3	HIV-1 Tat	Microglia	24
NLRP3	HIV-1 Vpr	Microglia	25
NLRP3	ROS	$CD4^+$ T	26,27
IFI16	HIV-1 incomplete reverse transcripts	Tonsil $CD4^+$ T	28
CARD8	HIV-1 protease	$CD4^+$ T, MDM	29
NLRP1	Unknown	PBMC	30,31
NLRC4	HIV-1 gp41	DCs, MDM	21
AIM2	Unknown	PBMC	30,32

NLRP3: NLR family pyrin domain-containing protein 3; IFI16: Interferon-inducible protein 16; CARD8: Caspase recruitment domain family member 8; NLRP1: NLR family pyrin domain-containing protein 1; NLRC4: NLR family CARD domain-containing protein 4; AIM2: Absent in melanoma 2; HIV-1: Human immunodeficiency virus type 1; ROS: Reactive oxygen species; PBMC: Peripheral blood mononuclear cell; DC: Dendritic cells; MDM: Monocyte-derived macrophage.

NLRP3 inflammasome activation by HIV-1 in monocytes and macrophages has been thoroughly studied. It has been proposed that viral RNA may trigger NLRP3 inflammasome activation. In addition, previous studies suggest that HIV-1 infection promotes pro–IL-1β expression via Toll-like receptor 8 and then induces IL-1β production through the NLRP3 inflammasome in monocytes, macrophages, and microglia cells.[17,19,20] More recently, it has also been reported that transfection of dendritic cells or peripheral blood mononuclear cells with HIV-1 single-stranded RNA (ssRNA) results in protein kinase R activation and downstream IL-1β production via NLRP3 inflammasome activation.[18] These studies suggest that HIV-1 RNA may trigger the generation of ROS or the release of protease cathepsin B through different mechanisms, contributing to NLRP3 activation. However, the specific HIV-1 transcript required for NLRP3 inflammasome activation during HIV-1 infection still remains unclear. It should also be noted that transfection of ssRNA may have limited *in vivo* relevance, as it is different from natural HIV infection that ssRNA is typically not exposed in the incoming viral particle because of protection by the capsid coating.[35,36] In addition, HIV-1 infection triggers NLRP3 and NAIP/NLRC4 inflammasome activation in monocyte-derived macrophages.[21] This suggests that IL-1β induction by HIV-1 viral protein U is regulated through the NLRP3 inflammasome, whereas IL-18 release by HIV-1 envelope glycoprotein gp41 is regulated via the NAIP/NLRC4 inflammasome.[21] Furthermore, many studies have reported NLRP3 inflammasome activation in microglia, which has been implicated in HIV-1–associated neurocognitive disorders. Multiple viral proteins have been described for NLRP3 inflammasome activation in microglia, including envelope glycoprotein gp120, transactivator of transcription (Tat), and viral protein R.[22–25] For instance, transfection of HIV-gp120 or Tat into microglia triggers NLRP3 activation and IL-1β production. Gp120 mediates NF-κB activation, which upregulates NLRP3 and pro–IL-1β levels, which in turn activates the NLRP3 inflammasome through K^+ efflux. By contrast, Tat activates NLRP3 by inhibiting miR-223 degradation of NLRP3.

Although HIV-1 can infect macrophages and microglia, which are associated with neurocognitive disorders,[37–40] $CD4^+$ T cells are the major targets of HIV-1 infection. Importantly, resting memory $CD4^+$ T cells make up the latent reservoir during HIV-1 infection.[41] Several previous studies have provided evidence in support of NLRP3 inflammasome activation in $CD4^+$ T cells during chronic HIV infection.[26,27] It has recently been reported that NLRP3 inflammasome activation plays a critical role in mediating the loss of $CD4^+$T cells in people living with HIV (PLHIV).[27] In this study, Zhang et al.[27] evaluated active caspase-1 and caspase-3 level in $CD4^+$ T cells from HIV-negative individuals, PLHIV who are viremic, PLHIV on antiretroviral therapy, and elite controllers. They observed that both apoptosis and pyroptosis occurred in $CD4^+$ T cells from PLHIV. More importantly, the authors demonstrated the contribution of the NLRP3 inflammasome to pyroptosis of $CD4^+$ T cells through ROS production, which is a predominant pathway for $CD4^+$ T cell loss during chronic HIV-1 infection.

Together, these studies reveal that the NLRP3 inflammasome is activated in HIV-1 targeted cells; however, exactly how NLRP3 senses HIV-1 and the key host factors that regulate NLRP3 activation in response to HIV-1 infection remain to be fully elucidated.

Sensing of HIV-1 through IFI16

IFI16 is a member of the interferon-inducible PYHIN protein family and includes a pyrin domain and two DNA-binding hematopoietic interferon-inducible nuclear (HIN) domains [Figure 1].[42] IFI16 has been described to act as a restriction factor for viral DNA by inducing STING-dependent interferon production, resulting in restriction of DNA virus and lentivirus replication.[42,43] IFI16 has also been reported as an inflammasome sensor that can sense viral DNA, leading to ASC-dependent inflammasome activation.[44,45]

In HIV-1, caspase-1 activation is implicated in cellular responses to abortive HIV-1 infection in $CD4^+$ T cells in secondary lymphoid tissues, indicating that inflammasome signaling plays an important role in $CD4^+$ T cell loss and progression to AIDS. It has been proposed that, in abortive HIV-1 infection of quiescent tonsillar $CD4^+$ T cells, incomplete HIV-1 reverse transcription products accumulate and are sensed by IFI16, which triggers caspase-1 activation and pyroptosis [Figure 1].[14,28] However, IFI16 is unable to sense abortive HIV-1 infection in peripheral blood $CD4^+$ T cells,[46] suggesting that other mechanisms may be involved in capsase-1 activation by HIV-1 in nonlymphoid resident $CD4^+$ T cells. Notably, IFI16 can bind to and inhibit Sp1, a host transcription factor, thus suppressing HIV-1 gene expression.[47] Thus, further studies are warranted to elucidate the confounding role of IFI16 in HIV-1 sensing and viral gene expression.

Sensing of HIV-1 through CARD8

CARD8 contains an N-terminal unstructured region followed by a function-to-find domain and a caspase activation and recruitment domain (CARD). CARD8 undergoes autoproteolytic processing between the ZU5 (found in ZO-1 and UNC5) and UPA (conserved in UNC5, PIDD, and ankyrins) subdomains of the function-to-find domain, which results in two noncovalently associated polypeptide chains: N terminal and C terminal fragments [Figure 1].[48,49] The dipeptidyl peptidase 8/9 inhibitor Val-boroPro (VbP) was shown to induce degradation of the N-terminal fragments in acute myeloid leukima–derived cell lines in a proteasome-dependent manner.[50] This results in the release of the C-terminal UPA-CARD domains and formation of the CARD8 inflammasome. DPP9 suppresses CARD8 activation through sequestration of the C-terminal fragment. Treatment with VbP results in CARD8 inflammasome activation because VbP induces N-terminal degradation and inhibits C-terminal fragment capture, resulting in disruption of the DPP9-ternary complex.[51] Importantly, CARD8 has been shown to play a role in inflammasome activation and pyroptosis of resting $CD4^+$ T cells through DPP9 inhibition.[52,53]

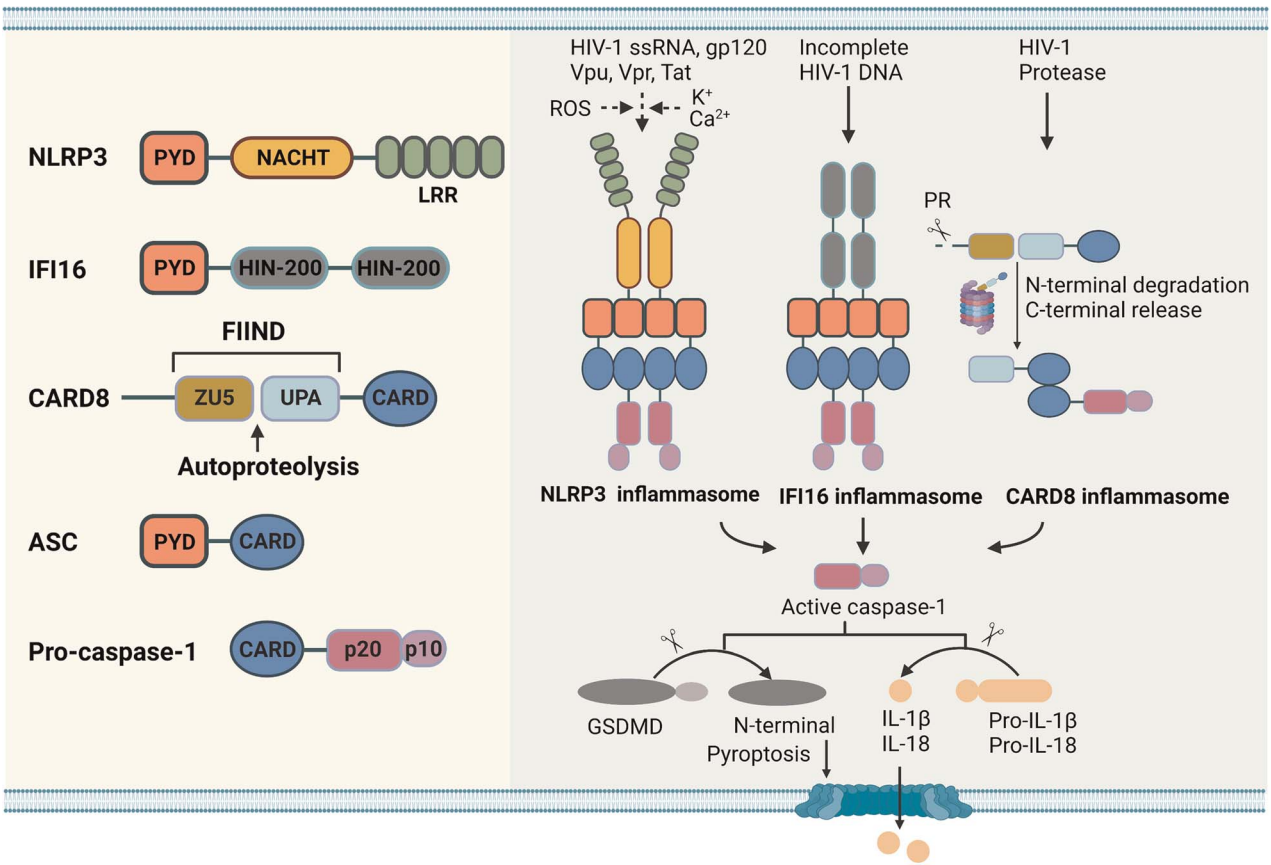

Figure 1: Inflammasome sensor for HIV-1. NLR family pyrin domain–containing protein 3 (NLRP3) encodes nucleotide-binding domain (NACHT)-, leucine-rich repeat (LRR)-, and pyrin domain–containing protein 3. Human immunodeficiency virus type 1 ssRNA and gp120, Vpu, Vpr, and Tat protein are involved in triggering NLRP3 inflammasome activation by inducing cytosolic K^+ efflux, cytosolic Ca^{2+} influx, or mitochondrial ROS production, resulting in ASC-dependent inflammasome assembly and caspase-1 activation. Interferon-inducible protein 16 (IFI16) contains a pyrin domain and two DNA-binding hematopoietic interferon-inducible nuclear (HIN) domains. During abortive human immunodeficiency virus type 1 (HIV-1) infection, incomplete HIV-1 reverse transcripts are sensed by IFI16, leading to ASC-dependent IFI16 inflammasome assembly, caspase-1 activation, and pyroptosis. Caspase recruitment domain containing protein 8 (CARD8) has an N-terminal unstructured region followed by a FIIND and a CARD. The FIIND undergoes autoproteolytic processing between ZU5 (found in ZO-1 and UNC5) and UPA (conserved in UNC5, PIDD, and ankyrins) subdomains, creating N-terminal and C-terminal fragments that remain noncovalently associated. HIV-1 protease directly cleaves the N-terminus of CARD8, generating an unstable neo-N-terminus, resulting in proteasome-mediated degradation of CARD8 to release of the bioactive C-terminal fragment and ASC-independent inflammasome assembly, leading to caspase-1 activation and pyroptosis. ASC: apoptosis-associated speck-like protein containing CARD; CARD: caspase activation and recruitment domain; FIIND: function-to-find domain; ROS: reactive oxygen species; ssRNA: single-stranded RNA; Tat: transactivator of transcription; Vpr: viral protein R; Vpu: viral protein U.

We recently reported that HIV-1 protease can directly cleave the N-terminus of CARD8, creating an unstable neo-N-terminus. The neo-N-terminus is targeted for proteasomal degradation, upon which the bioactive C-terminal fragment is released. This leads to inflammasome assembly, caspase-1 recruitment and activation, and pyroptosis.[29] In HIV-1–infected cells, the viral protease remains in an inactive state as a subunit of the Gag-Pol polyprotein precursor. We found that premature activation of intracellular HIV-1 protease by nonnucleoside reverse transcriptase inhibitors (NNRTIs) triggers CARD8 inflammasome activation and mediates killing of HIV-infected macrophages and $CD4^+$ T cells.[29]

As HIV-1 protease directly activates CARD8 in both macrophages and $CD4^+$ T cells, it will be of interest to investigate how the host regulates CARD8 inflammasome activation and whether natural HIV-1 infection can activate CARD8. Furthermore, unlike the other inflammasome sensors that have been identified and characterized in macrophages, burgeoning evidence shows that the CARD8 inflammasome can be activated in T cells.[29,52,53] Further studies are needed to better understand and compare the physiological role of CARD8 in T cells and macrophages.

Sensing of HIV-1 through other inflammasomes

Some studies have demonstrated that other inflammasomes might also have an impact on HIV-1 infection, such as NLR family pyrin domain–containing protein 1 (NLRP1), NLR family CARD domain-containing 4 (NLRC4), and absent in melanoma 2 (AIM2). Several groups have demonstrated that NLRP1 expression is associated with $CD4^+$ T cell loss.[30,31] NLRC4 has been reported to play a role in dendritic cells from PLHIV and also in monocyte-derived macrophages during HIV-1 infection.[21,54] Furthermore, increased AIM2 expression has been reported in the course of HIV-1 infection.[30,32] Nonetheless, the strong supporting evidence for activation of these inflammasomes warrants further study of their action during the course of HIV-1 infection.

Targeting the inflammasome for the treatment of HIV-1 infection

Despite antiretroviral therapy (ART) effectively suppressing HIV-1 in PLHIV, ART cannot eliminate HIV-1–infected cells, allowing lifelong persistence of HIV-1 latent reservoirs. This reservoir of

latently infected resting CD4+ T cells is the major barrier to a functional HIV cure.[41,55–57] Inspired by the results from animal model studies and a few clinical cases of HIV cures, several strategies have been proposed for HIV cure research, including cell and gene therapy, targeting the provirus by enhancing the function of immune cell.[58,59] One strategy for HIV-1 latent reservoir eradication called "shock-and-kill," involves induction of HIV-1 expression using latency reversing agents (LRAs), allowing latently infected cells to be exposed to viral cytopathic effects or clearance by the immune system.[60,61] However, LRAs alone are insufficient to induce cell death.[62–64] Thus, additional approaches to eliminate the latent reservoir are needed. We recently reported that targeting the CARD8 inflammasome may be a viable strategy to eliminate residual HIV-1–infected cells. We showed that premature activation of intracellular HIV-1 protease by NNRTI triggers CARD8 sensing and pyroptosis of HIV-infected macrophages and CD4+ T cells. In this study, we targeted an immutable component of viral protease function, which induced cell killing independent of apoptosis. More importantly, we found that CARD8 can recognize all subtypes of HIV-1 despite substantial viral diversity, which overcomes the challenge of the breadth of adaptive immune responses since the adaptive immune system only recognizes conserved epitopes.[29]

However, it is worth noting that there are at least two factors that may affect the strategy of targeting the CARD8 inflammasome. First, cells harboring transcriptionally silent HIV-1 do not express Gag-Pol, so potent LRAs are required to induce viral gene expression. Second, the clinically relevant concentration of NNRTIs may be suboptimal to trigger cell killing. Thus, more potent Gag-Pol dimerizers or drugs for sensitization of the CARD8 inflammasome are needed for this strategy. Based on this concept, our group recently found that DPP9 inhibition reduces the threshold concentration of NNRTIs needed to trigger pyroptosis in HIV-infected cells.[65] Another major obstacle for targeting the inflammasome for the treatment of HIV-1 infection is cytokine release during inflammasome activation. However, it is generally accepted that CD4+ T cells do not secrete the inflammatory cytokines IL-1β or IL-18. Moreover, the frequency of latently infected CD4+ T cells of PLHIV on ART is approximately 1 in 10^5 to 10^8 total CD4+ T cells.[66] Thus, CARD8-mediated pyroptosis of HIV-1–infected CD4+ T cells in PLHIV is not likely to cause excessive inflammation. Nonetheless, cytokine secretion of tissue macrophage reservoirs of HIV should be considered.[67]

It has been shown that targeting caspase-1 via specific inhibitor VX-765 can prevent lymphoid CD4+ T cell death, suggesting that blocking pyroptosis may be a therapeutic option to prevent CD4+ T cell loss.[14] In addition, because NLRP3 inflammasome activation in microglia has been implicated in HIV-1–associated neurocognitive disorders and other related complications, the development of therapeutic strategies aimed at targeting the NLRP3 inflammasome may be a promising direction to alleviate chronic inflammation.

Conclusion

Much has been learned about the interface between the inflammasome and HIV-1 infection in the past few years. This information demonstrates the role of inflammasome activation in HIV-1 pathogenesis and treatment. Nonetheless, several fundamental questions have yet to be answered. For instance, the exact ligand and mechanisms that activate NLRP3- and IFI16-mediated inflammasomes and which cell types they function within are still unknown. Moreover, more detailed studies are necessary to elucidate the mechanisms that regulate inflammasome functions. Investigating these questions will be key to informing the development of therapeutic strategies for the management and prevention of HIV-1 infection.

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Conflicts of Interest

None.

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