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Review

Role of the CARD8 inflammasome in HIV pathogenesis

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A B S T R A C T

Human immunodeficiency virus (HIV) continues to be a significant global health challenge despite decades of research and advances in treatment. Substantial gaps in our understanding of the mechanisms of HIV pathogenesis and the host immune responses still exist. The interaction between HIV and these immune responses is pivotal in the disease progression to acquired immunodeficiency syndrome (AIDS). Recently, the caspase recruitment domain-containing protein 8 (CARD8) inflammasome has emerged as a crucial factor in orchestrating innate immune responses to HIV infection and exerting a substantial impact on viral pathogenesis. CARD8 restricts viral replication by detecting the activity of HIV protease. Conversely, it also contributes to the depletion of $CD4^+$ T cells, a key feature of disease progression towards AIDS. The purpose of this review is to summarize the role of the CARD8 inflammasome in HIV pathogenesis, delving into its mechanisms of action and potential implications for the development of therapeutic strategies.

1. Introduction

HIV remains a global health issue, impacting millions of individuals. Recent statistics revealed that as of 2022, approximately 39 million people were living with HIV worldwide. Additionally, around 1.3 million new HIV infections were reported globally during the same year, highlighting the ongoing impact of this epidemic (UNAIDS, 2023). The hallmark of HIV pathogenesis is the progressive loss of $CD4^+$ T cells. As $CD4^+$ T cells decline, the immune system becomes less capable of combating common infections. This weakening of the immune defense ultimately facilitates the progression towards AIDS and its associated complications. The mechanisms by which HIV depletes $CD4^+$ T cells have been extensively studied for decades (Douek et al., 2003; McCune, 2001). Although HIV has direct cytopathic effects on infected cells, very few dying $CD4^+$ T cells are producing the virus (Finkel et al., 1995). Moreover, it is suggested that interaction with the virus, such as the engagement of the CCR5 receptor, prime cells for death without productive infection, which implies a mechanism where virus-cell interaction is required for $CD4^+$ T cell death (Brenchley et al., 2004; Grivel et al., 2000). This phenomenon is not restricted to human HIV infections but is also observed in pathogenic simian immunodeficiency virus (SIV) infections in rhesus macaques (Picker et al., 2004). In pathogenic models, especially in SIV-infected rhesus macaques, rapid inflammasome activation and subsequent pyroptotic cell death contribute significantly to $CD4^+$ T cell depletion (Barouch et al., 2016; He et al., 2022; Lu et al., 2016). Notably, SIV infections in some African non-human primate species like sooty mangabeys and African green monkeys do not lead to $CD4^+$ T cell loss or AIDS despite similar levels of viral replication (Chahroudi et al., 2012). Several studies suggest that aspects of the immune response, possibly including lower levels of chronic immune activation and microbial translocation, play protective roles in these species (Brenchley et al., 2006; Palesch et al., 2018; Silvestri et al., 2003). However, the specific mechanisms linking inflammasome activation to $CD4^+$ T cell depletion are not yet fully understood.

Our recent findings indicate that the CARD8 inflammasome plays a crucial role in bystander $CD4^+$ T cell depletion and disease progression in HIV infection. Additionally, we found that some "natural hosts" of SIV have acquired loss-of-function mutations in CARD8. These mutations may impair inflammasome assembly in response to the virus, which likely contributes to the non-pathogenic nature of SIV infections in these species (Wang et al., 2024).

In this review, we provide an in-depth exploration of the current understanding of the role of the CARD8 inflammasome in HIV pathogenesis. We detail the activation mechanism of the CARD8 inflammasome by HIV, discuss the implications of CARD8 loss-of-function in non-pathogenic SIV hosts, and explore the prospects of targeting the CARD8 inflammasome as a new therapeutic strategy to halt the progression of AIDS.

2. Mechanism of the CARD8 inflammasome activation in HIV infection

The inflammasome sensor protein CARD8 comprises a disordered N-terminus, a function-to-find domain (FIIND), and a caspase activation

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and recruitment domain (CARD). The FIIND domain consists of two subdomains, namely the ZU5 and UPA. Within the FIIND domain, CARD8 undergoes autoproteolytic cleavage, resulting in the separation of ZU5 and UPA, which remain non-covalently associated with each other (D'Osualdo et al., 2011; Taabazuing et al., 2020). This cleavage facilitates the proteasome-dependent degradation of the N-terminal fragment, freeing the C-terminal UPA-CARD fragment for inflammasome assembly (Gong et al., 2021; Robert Hollingsworth et al., 2021). The assembly is crucial for recruiting and activating caspase-1 (CASP1), which triggers pyroptosis, a lytic form of programmed cell death, and release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18 (Barnett et al., 2023; Broz & Dixit, 2016). To prevent unintended activation of the inflammasome pathway, CARD8 is sequestrated by dipeptidyl peptidases 8 and 9 (DPP8/9), which bind to CARD8 to form a suppressive complex. This interaction serves as a mechanism to control CARD8 activity under normal physiological conditions (Sharif et al., 2021). The intricate balance between the activation and inhibition of CARD8 ensures that it is activated only under certain stress or infection conditions, preventing excessive or unwarranted inflammation and cell death.

Understanding the role of CARD8 in human health and disease remains limited. Studies have indicated links between CARD8 polymorphisms and conditions such as inflammatory bowel disease and rheumatoid arthritis (Taabazuing et al., 2020). However, more comprehensive understanding is necessary to validate the functional relevance of these CARD8 mutations in autoimmune diseases. Several triggers have been reported to activate the CARD8 inflammasome, such as DPP9 inhibitors and viral proteases (Johnson et al. 2018, 2020; Linder et al., 2020; Nadkarni et al., 2022). We recently reported that HIV protease can cleave the N-terminus of CARD8, leading to an unstable neo-N-terminus. This newly formed N-terminus is then targeted for proteasomal degradation. Following degradation, the bioactive C-terminal fragment of CARD8 is released, which is essential for inflammasome assembly and activation of CASP1, and ultimately the initiation of pyroptosis (Wang et al., 2021). Interestingly, in cells already productively infected by HIV, the viral protease is present as a component of the Gag-Pol polyprotein precursor with minimal enzyme activity. Our findings demonstrate that the premature activation of intracellular HIV protease, induced by non-nucleoside reverse transcriptase inhibitors (NNRTIs), can trigger activation of the CARD8 inflammasome and pyroptosis of HIV-infected macrophages and $CD4^+$ T cells, providing a therapeutic intervention to reduce viral reservoirs (Clark, Kim, et al., 2023; Wang et al., 2021).

In follow-up studies, we demonstrated that natural HIV infection is also able to activate the CARD8 inflammasome and drive rapid $CD4^+$ T cell loss (Wang et al., 2024). We and others found that the CARD8 inflammasome was activated immediately after HIV entry by the viral protease encapsulated in the incoming HIV particle (Kulsuptrakul et al., 2023; Wang et al., 2024). Sensing of HIV protease activity by the CARD8 inflammasome led to rapid pyroptosis of quiescent $CD4^+$ T cells without productive viral infection, as cell death was observed within 4 h after exposure to HIV particles (Fig. 1). Additionally, humanized mice reconstituted with CARD8-deficient cells provided compelling evidence supporting the CARD8 inflammasome's role in HIV pathogenesis. These mice exhibited significantly delayed $CD4^+$ T cell depletion following HIV infection despite high levels of viremia, indicating that the CARD8 inflammasome contributes to the loss of $CD4^+$ T cells.

Additional inflammasome sensors besides CARD8 may be implicated during the HIV infection (Clark, Pal, et al., 2023; Doitsh et al., 2014; Wang & Shan, 2022). For example, IFI16 and NLRP3 have been identified as contributors to the HIV-induced pyroptosis of $CD4^+$ T cells (Monroe et al., 2014; Zhang et al., 2021). These studies showed that in quiescent tissue $CD4^+$ T cells, incomplete reverse transcription products of HIV accumulate and are detected by IFI16, leading to the activation of caspase-1 and subsequent pyroptosis. Additionally, HIV infection may stimulate production of reactive oxygen species (ROS) or cause the release of the protease cathepsin B via various mechanisms, which in turn activates the NLRP3 inflammasome. However, it is essential to consider that these inflammasomes are active mainly in specific subsets of $CD4^+$ T cells (Munoz-Arias et al., 2015). Furthermore, the detailed mechanisms by which IFI16 and NLRP3 drive pyroptosis in human T cells need to be thoroughly understood and investigated.

3. CARD8 loss-of-function in non-pathogenic SIV hosts

In our evolutionary studies of CARD8, we observed significant differences between the "natural" and pathogenic hosts of SIV. Specifically,

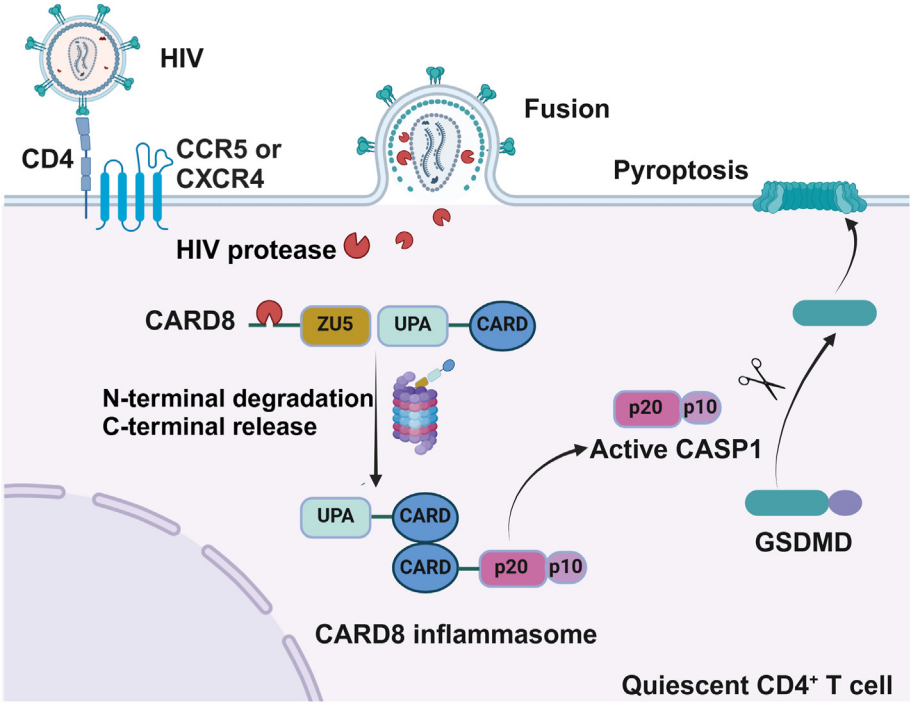

Fig. 1. Mechanism of CARD8 activation by HIV
Upon entering resting $CD4^+$ T cells, the HIV protease encapsulated within incoming viral particles immediately triggers the CARD8 inflammasome. This protease cleaves the N-terminus of CARD8, generating an unstable new N-terminus marked for proteasomal degradation. Consequently, the biologically active C-terminal UPA-CARD fragment of CARD8 is liberated, initiating the inflammasome assembly. This leads to the recruitment and activation of CASP1, ultimately resulting in GSDMD-dependent pyroptosis of the resting $CD4^+$ T cells.

the "natural" SIV hosts, such as sooty mangabey and African green monkey, exhibit various truncations in the CARD domain of the CARD8 protein due to large deletions or frameshift mutations, which disrupt its ability to interact with CASP1. By contrast, pathogenic hosts, including humans, chimpanzees, and rhesus macaques, have intact CARD8 open reading frames, allowing proper interaction with CASP1 and subsequent inflammasome assembly upon viral infection. Functional tests revealed that CARD8 from "natural" hosts did not trigger cell death, unlike those from pathogenic hosts. This difference was further evidenced in experiments using peripheral blood mononuclear cells from rhesus macaques and sooty mangabeys. While SIV infection led to significant $CD4^+$ T cell loss from rhesus macaques, it did not cause a depletion in cells from sooty mangabeys. These findings suggest that evolutionary adaptations in CARD8 by the "natural" SIV hosts contribute to the non-pathogenic nature of SIV infection in these species (Wang et al., 2024)

Given that rapid activation of inflammasome, followed by pyroptotic cell death, is a critical factor in $CD4^+$ T cell depletion during SIV infection in rhesus macaques (He et al., 2022; Lu et al., 2016), it would be intriguing to delve deeper into the role of CARD8 in the pathogenesis of SIV *in vivo*. Specifically, whether modulation of CARD8 through blockade, inhibition or targeted gene editing may impact the disease outcome. This would offer insights into the effects of CARD8 on SIV pathogenesis and disease progression.

4. Targeting the CARD8 inflammasome to prevent AIDS progression

Antiretroviral therapy (ART) is currently the standard treatment for HIV infection, effectively reducing the virus to undetectable levels and preventing the progression to AIDS (Landovitz et al., 2023; Mody et al., 2024). Nonetheless, some people living with HIV on ART experience an incomplete recovery of $CD4^+$ T cells, leaving them more susceptible to infections and other health issues (Gaardbo et al., 2012; Okoye & Picker, 2013). Since the CARD8 inflammasome contributes to $CD4^+$ T cell loss during HIV infection, targeting the CARD8 inflammasome represents a novel therapeutic approach to preventing disease progression. In addition, chronic inflammation and immune dysregulation are also hallmarks of HIV infection and are associated with several comorbidities, such as cardiovascular diseases, neurocognitive disorders, and accelerated aging (Heneka et al., 2018). Prolonged activation of CARD8 can potentially worsen the problem by continuously releasing pro-inflammatory cytokines like IL-1β and IL-18, further fueling chronic inflammation. By inhibiting CARD8, it may be possible to suppress the release of these cytokines and reduce chronic inflammation, thus offering a potential avenue for alleviating the associated health complications.

In summary, targeting the CARD8 inflammasome in HIV treatment could potentially reduce inflammation and improve $CD4^+$ T cell recovery, which is currently not adequately addressed by standard ART alone. Combining CARD8 inhibitors with existing antiretroviral drugs may lead to synergistic effects and enhance the overall management of HIV. For example, small molecules that precisely target CARD8 or disrupt its interactions within the inflammasome complex could preserve $CD4^+$ T cells and reduce inflammation. Moreover, exploiting endogenous regulators of CARD8, such as other cellular proteins that naturally inhibit CARD8 expression or function, could provide a new therapeutic strategy. This approach would not only control the virus but also mitigate immune dysregulation and inflammation, which are significant factors contributing to disease progression and comorbidities.

In addition to CARD8 inhibition, our earlier research demonstrated that treatment with NNRTI, either alone or combined with DPP9 inhibitor to activate the CARD8 inflammasome, can effectively clear latently infected cells in people living with HIV upon reactivation (Clark, Kim, et al., 2023; Wang et al., 2021). Given that Rilpivirine has received FDA approval as part of a long-acting injectable treatment regimen, further investigation is needed to determine whether NNRTI can activate the CARD8 inflammasome and consequently reduce viral reservoirs *in vivo*.

5. Conclusions

The CARD8 inflammasome plays a crucial role in HIV/SIV pathogenesis and disease progression. Its ability to sense HIV protease activity can aid in viral clearance and control viral replication. However, it is important to note that CARD8 also contributes to the depletion of $CD4^+$ T cells, ultimately leading to the progression to AIDS. Further research into the molecular mechanisms of CARD8 activation and its function is essential in order to develop novel therapeutic approaches that have the potential to revolutionize HIV treatment strategies. Moreover, understanding the involvement of CARD8 in chronic inflammation and exploring how CARD8 inhibitors can be used in combination with ART to offer synergistic effects, ultimately leading to better control of HIV-associated inflammation and immune reconstitution.

CRediT authorship contribution statement

Qiankun Wang: Writing – review & editing, Writing – original draft, Conceptualization. **Liang Shan:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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