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REVIEW ARTICLE

Adenosine signaling and adenosine deaminase regulation of immune responses: impact on the immunopathogenesis of HIV infection

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Abstract

Infection by human immunodeficiency virus (HIV) causes the acquired immune deficiency syndrome (AIDS), which has devastating effects on the host immune system. HIV entry into host cells and subsequent viral replication induce a proinflammatory response, hyperactivating immune cells and leading them to death, disfunction, and exhaustion. Adenosine is an immunomodulatory molecule that suppresses immune cell function to protect tissue integrity. The anti-inflammatory properties of adenosine modulate the chronic inflammation and immune activation caused by HIV. Lack of adenosine contributes to pathogenic events in HIV infection. However, immunosuppression by adenosine has its shortcomings, such as impairing the immune response, hindering the elimination of the virus and control of viral replication. By attempting to control inflammation, adenosine feeds a pathogenic cycle affecting immune cells. Deamination of adenosine by ADA (adenosine deaminase) counteracts the negative effects of adenosine in immune cells, boosting the immune response. This review comprises the connection between adenosinergic system and HIV immunopathogenesis, exploring defects in immune cell function and the role of ADA in protecting these cells against damage.

Keywords HIV infection · Adenosine · Adenosine deaminase · Inflammation

Introduction

Purine metabolism is involved in a series of physiologic and pathologic events in cells and tissues. Extracellular nucleotides and nucleoside are signaling molecules that act in an autocrine and paracrine way. Under stress, cells release adenosine triphosphate (ATP) to the extracellular medium, which activates P2 purinergic receptors triggering an inflammatory response. ATP levels are controlled by purinergic enzymes: E-NTPDase (EC 3.6.1.5; CD39) converts ATP into ADP (adenosine diphosphate) and AMP (adenosine monophosphate) and E-5′-nucleotidase (EC 3.1.3.5, CD73) converts AMP to adenosine. Adenosine suppresses the proinflammatory response and promotes an anti-inflammatory response through P1 purinergic receptors [1]; this shift ensures protection against tissue damage [2]. However, accumulation of adenosine leads to immunosuppression in cancer [3, 4] and infection [5, 6]. Adenosine deaminase (ADA) (EC 3.5.4.4) controls the extracellular levels by converting adenosine into inosine [6]. A delicate balance is sustained by restraining inflammation while containing excessive immunosuppression.

The first cases of acquired immune deficiency syndrome (AIDS), a consequence of human immunodeficiency virus (HIV) infection, appeared in the early 1980s. Since then, research has come a long way unveiling major aspects of HIV pathogenesis along with developing diagnostic and monitoring tools, as well as effective antiretroviral therapy. Nevertheless, HIV genetic variability and host response evasion mechanisms are major challenges for vaccine development and the complete eradication of the virus. HIV targets

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immune cells by infecting them directly or indirectly causing systemic changes that will affect their function. Despite successful suppression of viremia, chronic inflammation and immune activation persist indicating that immune function is not completely restored by antiretroviral therapy [7, 8]. The purpose of this paper is to review the interface between adenosine signaling and the immunopathogenesis of HIV infection and discuss the effects of adenosine deaminase activity on the HIV-induced immune dysfunction.

Adenosine pathway and immunosuppression

Adenosine-mediated immunosuppression may be beneficial in inflammatory diseases such as autoimmunity, cancer, and infection, promoting tissue protection and regeneration [9]. In fact, low concentrations of adenosine are found in the extracellular environment in physiologic conditions. Upon hypoxia, tissue damage, inflammation, infection, or other causes of stress, adenosine is produced as a consequence of ATP dephosphorylation [10–12]. Extracellular adenosine is mainly generated via the CD39/CD73/adenosine pathway, which is activated by high levels of extracellular ATP. Adenosine interacts with adenosine receptors, called P1 receptors, in different types of cells in a variety of tissues, such as heart, brain, and immune system. There are four known types of P1 receptors, A1, A2A, A2B, and A3 [12]; all of them are expressed in immune cells [9]. A2A receptors are key players in the immunomodulatory actions of adenosine to maintain a balance between inflammation and suppression of overactive immune cells [13]. Activation of A2A receptors downregulates the release of proinflammatory mediators and upregulates the release of anti-inflammatory regulators. A2A receptor inhibition extensively affects the immune response, from antigen presentation to T cell activation, expansion, and function [14]. A2A receptors are more directly linked to the suppressive/anti-inflammatory effects of adenosine, while A2B also acts as an anchoring molecule to ADA and improves immune responses [15].

An important mechanism involved in the immunosuppressive effects of adenosine is the production of cyclic AMP (cAMP) by adenyl cyclases (AC). cAMP modulates several processes including the immune response as it influences function, proliferation, and activation of immune cells. Increased adenosine levels raise cAMP production via A2A and A2B receptors, which regulate its own release in immune cells. Elevated levels of cAMP, upon inflammatory and toxic stimuli, are known to have immunosuppressive effects [16, 17].

Adenosine impacts the function, proliferation, and activation of immune cells, modulating and polarizing immune responses. These immunomodulatory effects reflect adenosine-induced changes in the expression of surface molecules and release of chemokines and cytokines by immune cells [18–20].

Taken together, upregulation of adenosine and adenosine receptors, and consequent increase in cAMP levels, represent an efficient mechanism of limitation and resolution of inflammation.

Immune response and immunopathogenesis of HIV

Innate and adaptive responses are involved in host defense against HIV. Despite efforts to eradicate the infection, host response is only capable of reducing viral replication and, temporarily, delays the effects of infection. During the course of infection, HIV deploys several evading mechanisms by impairing host response, hiding in reservoirs and securing its own survival and replication [21, 22].

The innate immune response plays an important part in the host response by reducing replication during the acute phase of infection. Pattern recognition receptors (PRRs) recognize viral particles on the surface of monocytes, macrophages, dendritic cells (DCs), and neutrophils, prompting the release of inflammatory mediators. Natural killer (NK) cells are stimulated and detain the virus through cytolytic action and release of cytokines. DCs activate T cells eliciting the assembling of a Th1 response [23–25]. Lately, greater attention has been directed to the role of myeloid cells and innate immune response in antiviral response and pathogenesis of HIV infection [24, 26–29]. DCs and neutrophils modulate T cell function and proliferation [29]. $CD4^+$ T cells activate B cells, which in turn secrete antibodies to neutralize the virus. Cytotoxic effects of $CD8^+$ T cells control disease progression [30].

HIV specifically targets $CD4^+$ T cells [31], but also infects macrophages [32] and DCs [33]. Several other sets of immune cells are affected by the virus: $CD8^+$ T cells [34], monocytes/macrophages [32, 35, 36], B lymphocytes [37], neutrophils [38], natural killer (NK) cells [39], and platelets [40]. In fact, HIV impairs cells that are involved in the host response against itself.

The hallmarks of HIV infection are a progressive loss of the $CD4^+$ T cell pool [31], chronic inflammation, and persistent immune activation, which represent the immunopathogenic triad of HIV infection [41] (Fig. 1). Loss of the protective barrier in the intestinal mucosa, caused by depletion of $CD4^+$ T cells, allows leakage of bacterial products into the bloodstream, activating the innate immune system [42]. The fast cell turnover induced by chronic inflammation and activation results in exhaustion of HIV-specific $CD8^+$ T cells [41].

Adenosine and the immunopathogenesis of HIV

Purine metabolism is involved in the onset of HIV infection as well as in the maintenance of inflammation and immune

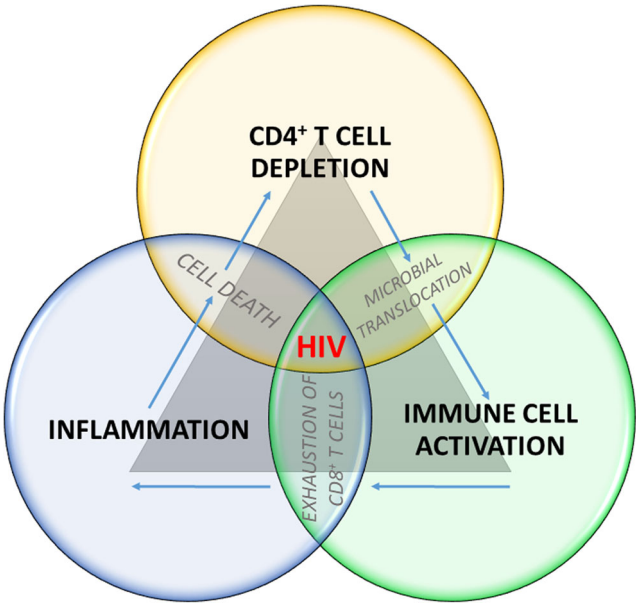

Fig. 1 Immunopathogenic triad of HIV infection: $CD4^+$ T cell depletion, inflammation, and immune activation are key elements in the pathogenesis of HIV infection. Viral replication drive $CD4^+$ T cell death, creating a proinflammatory environment. Gut $CD4^+$ T cell depletion leads to microbial translocation that culminates in immune cell activation. Chronic inflammation and persistent immune activation drives the $CD8^+$ T cell pool to exhaustion. This sequence of intertwined processes characterizes the pathogenic cycle of HIV infection

activation. P2Y2 and P2X1 receptors enable viral entry [43, 44], and the latest is also involved in viral replication as well as P2X7 and P2Y1 [44]. When viral proteins bind to macrophages or $CD4^+$ T cell receptors, ATP is released via pannexin channels, stimulating P2X7 receptor [44, 45]. Subsequent influx of potassium activates the NLRP3 inflammasome that leads to cell death [46, 47]. A recent study has proposed that caspase-1 pathway is an important mechanism of $CD4^+$ T cell depletion by HIV infection, promoting cell death by pyroptosis [48]. Assembly of the inflammasome stimulated by IL-1 secretion is an important part of the antiviral response [46]; a mechanism seized by HIV in order to kill its target cells [48]. Extracellular ATP released by infected cells is degraded by CD39, which is overexpressed and has increased activity during HIV infection [49, 50]. Upregulation of CD39 is associated with HIV disease progression [49]. The effects of CD39 on T cells will be discussed in an upcoming section of this paper. Figure 2 summarizes the purinergic cascade in HIV infection.

In contrast to murine Tregs, human Tregs rarely coexpress CD4, CD39, and CD73, which is quite intriguing because it contradicts the fact that these cells produce adenosine. But a recent work has shown that CD73 found in exosomes are a source of membrane-tied CD73 that might be used by Tregs to produce adenosine [51]. The expression of CD73 is even lower in different T cell subsets in HIV-infected patients when compared to healthy individuals [18, 52].

A study with simian immunodeficiency virus (SIV) has shed further light on the importance of adenosine pathway on disease progression [53]. The use of animal models allowed the study of non-progressive and progressive infection, and several parameters were compared between them. As expected, adenosine was shown to suppress inflammation but, unlike in HIV infection, CD39/CD73 coexpression is increased in $CD4^+$ Tregs upon SIV infection. No changes in adenosine levels were observed in lymph nodes, but higher levels were found in the gut mucosal of non-progressive animals when compared to progressive ones. This suggests that elevated adenosine levels are involved in controlling inflammation and immune activation in the gut, exerting an important function of halting disease progression [24]. Further studies are necessary to understand the role of adenosine in HIV. Adenosine is a signaling molecule that could be used as therapy to contain inflammation, as long at its detrimental effects are fully understood and controlled [54].

Adenosine signaling pathway impact on different immune cells during HIV infection

Lymphocytes are very important cells when it comes to immune response to HIV, and, undoubtedly, most damage is inflicted on these cells. However, besides lymphocytes, HIV affects the function of several other immune cells, which may interfere with lymphocyte proliferation, activation, and function. Many immune cells, as they react to a stressor such as HIV, produce adenosine and cAMP causing changes in their own actions and, by altering the microenvironment, affect other cells. On this section, we describe how HIV impairs activation, function, and survival of immune cells, either by affecting the cells directly or indirectly by interfering with the crosstalk between them. We also discuss the physiologic and pathologic role of adenosine and cAMP in each cell type.

Neutrophils

Neutrophils are the first line of defense against pathogens. They are recruited from the bloodstream to the site of inflammation where they engage in phagocytosis, degranulation, and release of NETs (neutrophil extracellular traps). These cells generate ATP and adenosine and express P1 receptors, which in turn regulate several of their functions. Adenosine and adenosine receptors have been implicated in neutrophil chemotaxis [55–57], adhesion, phagocytosis, and oxidative burst [58].

It has been proposed that neutrophils detect HIV via Toll-like receptors (TLR), producing reactive oxygen species (ROS) and forming NETs to eliminate the virus. HIV also activates host neutrophils by modulating TLR expression,

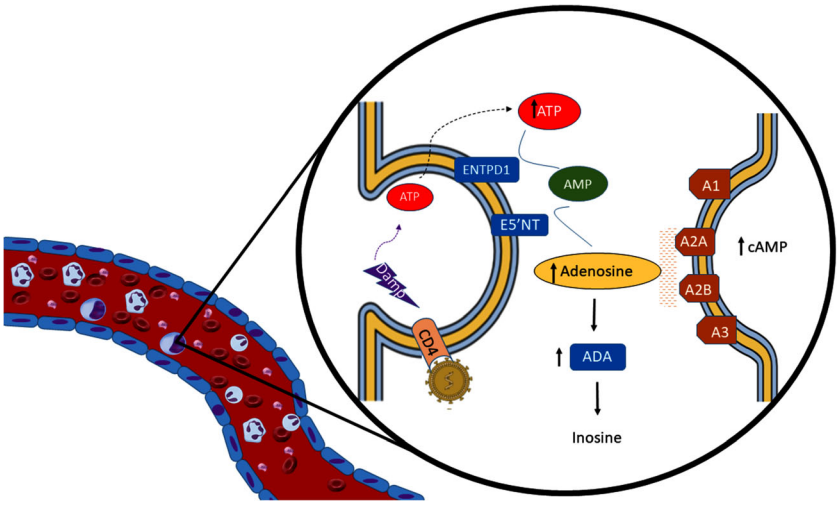

Fig. 2 Infection by HIV induces changes in immune cells, generating immunosupressive adenosine and cAMP. Purinergic signaling begins with ATP release into the extracellular milieu in response to HIV gp120 binding to CD4 receptor. ATP is converted into adenosine by ectonucleoside triphosphate diphosphohydrolase-1 (ENTPD1, CD39) e ecto-5′-nucleotidase (E5′NT, CD73). Elevated adenosine levels increase the expression of adenosine receptors. When adenosine is bound to A2A and A2B, cAMP levels are raised. ADA adenosine deaminase, cAMP cyclic AMP

inducing the production of IL-6, TNF-α, and ROS, exacerbating inflammation and downregulating T cell function [59]. An indirect effect of HIV on neutrophils is the stimulation of IL-1 production by DCs, inhibiting NET formation and evading the immune response [60]. In HIV-positive patients, concomitant overexpression of PD-L1 in neutrophils and PD-1 in T cells has been shown to result in downregulation of T cell proliferation and ROS production, further enhancing immunosuppression [28].

Monocytes/macrophages

Macrophages are terminally differentiated cells originated from monocytes. They are phagocytes and APCs involved in the innate and adaptive responses. P1 receptors modulate monocyte differentiation and macrophage function via cAMP. Once exposed to increased c-AMP levels and proinflammatory cues, monocytes augment their production of IL-6 and IL-10 and decrease the production of TNF-α, leading to differentiation and an activated macrophage-like phenotype [16]. A2B receptor expression on macrophages is upregulated by proinflammatory cytokine IFN-ɣ, activating adenyl cyclase and leading to higher levels of cAMP, reducing macrophage proliferation, and contributing to their loss of function [61]. cAMP is involved in macrophage phagocytosis impairment in HIV infection [62] and stimulates replication of latent virus residing in monocyte/macrophages [63].

In the context of HIV infection, monocytes and macrophages are infected, but unlike $CD4^+$ cells, they are not submitted to depletion and act as reservoirs for the virus [35, 64]. Phagocytosis, pathogen killing, chemotaxis, and cytokine production are impaired by HIV [36]. Purine metabolism is an important pathway in the establishment and persistence of HIV infection. The release of ATP to the extracellular milieu is triggered by the contact of HIV proteins with macrophage surface receptors and activates P2 receptors. The activation of these receptors starts a cascade of reactions which are involved in different stages of infection. P2X1 activation was shown to be essential for viral entry, while other P2 receptors are involved in later events of the viral cycle [44]. In addition, a recent study has shown that extracellular ATP may prompt the release of virions from macrophages [65]. ATP release is known to trigger the purinergic cascade, but the roles of CD39, CD73, and adenosine in macrophages are yet to be explored in the context of HIV infection.

Platelets

Apart from controlling bleeding and keeping homeostasis, platelets take part in tissue recovery and response against pathogens, since activated platelets modulate immune responses through recruitment and release of inflammatory mediators [66]. New roles for these cells in HIV infection were proposed recently. While one study showed that platelets may release antiviral factors in an attempt to suppress the virus as it enters the organism [67], another work suggested that HIV is internalized by platelets, favoring cell-to-cell dissemination and persistence [68].

The antithrombotic effect of adenosine is accounted for its ability to inhibit platelet activation via A2A and A2B receptors leading to increased cAMP [69]. Despite the protective role of platelet activation in tissue healing, chronic activation

and interaction with other immune cells might be detrimental, exacerbating inflammation [70]. Platelet activation and increased platelet aggregation lead to thrombocytopenia in inflammation, which is also observed in HIV-infected patients [71]. Inflammation and platelet interaction with endothelial cells may explain the increased risk of cardiovascular diseases in HIV positive patients [70, 72].

Dendritic cells

Dendritic cells are responsible for processing antigens, presenting them to T cells and activate T-naïve cells towards a Th1 response, therefore linking innate and adaptive immune responses. The role of DCs in eliciting adaptive immune is impaired by HIV. Instead, the virus infects DCs facilitating transfer to $CD4^+$ T cells taking advantage of DC-T cell interaction [33].

Adenosine, through adenosine receptors, affects chemotaxis, differentiation, and activation of DCs. A1 receptors induce chemotaxis in immature DCs, facilitating migration towards the sites of inflammation. When DCs are stimulated by contact with pathogens, they produce IFN-ɣ, IL-6, and IL-12, prompting T cell activation. In mature DCs, adenosine via A2B receptors downregulates the production of these cytokines, impairing DC function [73]. Activation of A2B receptors and the resultant increase in cAMP, in mature DCs, affects their own immunogenicity and indirectly regulate T cell function [74]. In the presence of adenosine, the capacity of DCs to induce proliferation of T cells is reduced [75, 76]. By reducing DC immunogenicity, cAMP might decrease the transfer of HIV, hindering effective infection. However, once the infection is established, by downregulating T cell function, c-AMP may further impair T cell response [74].

NK cells

NK cells recognize pathogens and exert their cytotoxic and cytolytic effects, thereby combating infection. Interplay with DCs resulting in activation and enhancing of their effector function as well as DC activation and maturation [25]. Impairment of NK cells by HIV infection, as well as disruption of the crosstalk between NK cells and DCs, results in loss of quality of the adaptive immune responses. The mechanisms of which NK cells recognize HIV-infected cells are not well-established to date, but some of them include the expression of important ligands for activating NK cell receptors on infected cells or cross-linking of CD16 mediated by binding of antibodies to HIV-infected cells [25]. The functional deficiency of NK cells during HIV infection is attributed to the reduced cytotoxic capacity, incomplete activation, relocation, an altered balance of NK cells responses, and less responsiveness to type I interferons, which is necessary to NK cytotoxicity and proliferation. All these changes in the functionality of NK cells, combined with a compromised DC function result in deregulation of the crosstalk between NK cells and DCs during HIV infection [25, 39, 77].

A2A adenosine receptor signaling has been implicated in adenosine-mediated inhibition of cytokine production and cytotoxic activity by activated NK cells. The suppression of cytotoxicity seems to be a result of the adenosine interference that affects the process of granule exocytosis. On the other hand, A1 receptor agonists are related to the enhancement of NK cell-cytolytic function [2].

T cells

Regulatory T cells (Tregs) are crucial in controlling chronic inflammation by mediating T cell suppression dependently and independently of APCs [78]. Tregs produce extracellular adenosine, which mediates immunosuppression by downregulating immune responses. The increase of adenosine levels is one of the underlying mechanisms involved in Treg function, which affects a wide range of immune cells such as $CD4^+$ and $CD8^+$ T cells, DCs, B cells, macrophages, natural killer (NK), and mast cells [79].

By accessing the sites of inflammation, Tregs block effector cells generating adenosine from 5′-AMP produced by neutrophils for example [80]. Hence, inflammatory cytokines such as IL-10 and TGF-β are released [79], and the secretion of proinflammatory cytokines IL-12 and TNF-α [19] is reduced.

Adenosine signaling via A2A receptors in Tregs activates adenyl cyclases generating cAMP [81]. Expansion of Tregs and A2A receptors signaling increase the intracellular levels of cAMP, which seems to play an important role on adenosine-mediated immunosuppression [12, 82]. Immunosuppression by Treg mediators impairs the immune response to pathogens and cancer [54]. In fact, the upregulation of A2A receptors and CD39 in Tregs blocks the production of inflammatory mediators IFN-ɣ, TNF-α, and IL-2 in HIV-infected patients [49]. CD39 expression in Tregs is involved in suppression of $CD8^+$ T cell proliferation in HIV infection. Taken together, these findings prove that this pathway is directly involved in the immunosuppressive effects observed in these patients [49].

$CD4^+$ and $CD8^+$ T cells express A2A receptors, and their activation increases the expression of these receptors. There is evidence of preferential depletion of the $CD4^+$ $CD73^+$ T cell pool during HIV infection, independently of viral load levels. Even as $CD4^+$ T cell counts normalize, this specific subset does not recover. Lower counts of $CD4^+CD73^+$ T cells reduce adenosine-induced suppression and favor persistent immune activation [18]. Expression of CD73 by $CD8^+$ T cells is

downregulated in HIV infection and also correlates with immune activation and disease progression [52]. In conclusion, CD39, CD73, and A2A receptor expression are critical players in effector T cell inhibition and their disrupted function during HIV infection [83].

Chronic exposure to adenosine is related to replicative senescence in $CD8^+$ T cells, causing progressive loss of CD28, a costimulatory molecule involved in T cell response initiation, affecting T cell proliferation, and reducing the activity of telomerase [84], an enzyme responsible for maintaining telomere length during $CD8^+$ T cell expansion in viral infections [85]. These changes not only favor disease progression but also premature aging in HIV-infected individuals [84, 86].

Though low levels of adenosine are produced by these cells, the microenvironment exposes them to adenosine released by several other cells. High levels of adenosine critically affect the function of activated T cells through A2A receptors, impairing their cytokine production and cytotoxic action [87–89]. Activated T helper (Th) cells have their production of IL-2, IL-4, IFN-γ, and TNF-α significantly reduced [13]. Migration into sites of inflammation is also inhibited by adenosine signaling [90]. T cell activation, proliferation, and cytokine production are also affected by cAMP, and the signaling cascades are triggered by it [17, 74]. HIV-infected $CD4^+$ T cells exhibit amplified A2A expression, increased intracellular cAMP levels, and reduced expression of IL-2 when stimulated, resulting in immunosuppression [91].

B cells

B cells are activated by HIV replication preventing them from delivering a robust antigen response. HIV shortens their replication and proliferation, reduces their diversity, and relocates them away from T cells preventing their interaction [37]. $CD4^+$ T cell depletion, inflammation, and chronic immune activation drive B cells to exhaustion, which results in an attempt to overcome the harmful effects of exacerbated immune activation by elevating expression of inhibitory receptors which make these cells unresponsive [37, 92].

Production of IL-10, as well as other anti-inflammatory mediators, is a characteristic of B regulatory cells or Bregs, which modulate T cell response by downregulating T cell proliferation and cytokine production [93]. This mechanism has been described in HIV-untreated infection, where Breg numbers are elevated and correlate directly with viral load and inversely with T cell response. It has been suggested that HIV may upregulate differentiation of Breg cells as an immune response evasion strategy [94]. Another mechanism of T cell response impairment by B cells is through adenosine. Activated B cells have shown to augment CD39 expression and decreased CD73 expression, modulating T cell responses via 5′AMP and adenosine, which has autocrine and paracrine effects via different P1 receptors [95]. However, in the context of HIV infection, activated B cells have demonstrated downregulation of CD73 and reduced adenosine production in untreated patients, which is related to low $CD4^+$ T cell counts and antibody class switch, showing that a decrease in adenosine levels are just as harmful as an increase [96]. There seems to be a connection between IL-10 production and adenosine since $IL\text{-}10^{-/-}$ B cells show a reduced adenosine production due to decreased CD73 production, but further studies are necessary to elucidate these mechanisms [97].

In conclusion, we highlight that the crosstalk among immune cells is essential for an effective response since the mounting of an immune response does not depend on the activation and function of a single type of cell.

ADA influences immune responses

ADA deficiency or loss of activity leads to immunodeficiency and results in accumulation of adenosine accompanied by serious immune dysfunction such as in severe combined immunodeficiency (SCID) [98]. Lymphocytopenia, characteristic of ADA deficiency, suggests that ADA has an important role in lymphocyte proliferation [99].

Downstream metabolism of adenosine plays an important role in balancing the immunosuppressing effects of adenosine by controlling its extracellular levels. Enzymatic function of ADA controls adenosine levels by irreversibly deaminating adenosine and deoxyadenosine into inosine. Adenosine deamination is performed by two different enzymes, ADA1 and ADA2, which were recently found to bind to distinct immune cells subsets. ADA1 binds to T and natural killer T (NKT) cells, while ADA2 binds to cells that do not express CD26: B cells, neutrophils, monocytes, NK, and CD26-Tregs [100]. ADA2 was previously shown to be secreted by monocytes and DCs [11].

In the context of inflammation, plasma levels of ADA are raised in response to increased levels of adenosine. Production of cytokines by neutrophils and monocytes is restored with elevated concentration of plasmatic ADA2. ADA2 has also an impact on Treg function inhibiting adenosine-mediated activation of these cells [100]. Improvement in Treg generation is also encouraged by deamination of adenosine, as well as memory and effector T cells [101, 102]. Since higher ADA activity is also found in monocytes/macrophages during intracellular infections upon release of adenosine, it is assumed that serum ADA is mostly originated from these cells. Similarly, serum and plasma are rich in ADA2, which is expressed in the surface of these cells [103, 104].

In addition to enzymatic activity, extracellular ADA acts as a costimulatory molecule by binding to CD26 and to A1 and A2B adenosine receptors [105]. This non-enzymatic activity plays a great part in the role of ADA in the immune system.

Ecto-ADA may bind to two distinct anchoring proteins: CD26 and adenosine receptors A1 and A2B. A costimulatory signal is triggered when ADA attached to DC surface through A2B receptors binds to CD26 on the surface of T cells. It occurs independently of enzymatic activity and activates T cells [106], enhances the generation of effector T cells, and boosts memory T cell generation [101]. Addition of ADA to cultured DCs with heat-inactivated HIV and T cells has been shown to enhance T cell proliferation and cytokine production [107].

ADA boosts monocyte-derived DCs from HIV-infected patients and healthy individuals, and it happens due to both enzymatic and non-enzymatic activities. It also promotes maturation of DCS, enhances its costimulatory capacity, and polarizes the immune response towards Th1 by stimulating the release of IL-12, TNF-α, and IL-6 [108].

ADA may increase the costimulatory potential of DCs. Another interesting aspect to highlight is that the addition of ADA to immature DC cultures increases Th-1/proinflammatory cytokine release including IL-12, TNF-α, and IL-6. ADA2 increases proliferation of monocyte-activated $CD4^+$ T cells independently of its catalytic action, as well as the differentiation of monocytes into macrophages induced by T cells, and stimulation of macrophage proliferation [11].

Taken together, all this data plus the fact that ADA is already commercially available suggests that ADA would be an effective adjuvant for DC-based and DNA-based anti-HIV vaccine [102, 109].

ADA in the context of HIV pathogenesis

Viral glycoprotein gp120 initiates HIV cell cycle by binding to the CD4 receptor and coreceptors on the surface of the host cell, triggering cell membrane modifications followed by fusion of host and viral membranes [110]. This glycoprotein prevents the interaction between ADA and CD26, which is a costimulatory signal for TCR-mediated T cell activation [111, 112]. This inhibitory effect was described in $CD4^+$ and $CD4^-$T cells, being independent of gp120 binding to CD4 [112]. It seems to be implicated in the impairment of T cell response by HIV. Martinez-Navio et al. (2009) have demonstrated that T cell proliferation is decreased in HIV-infected patients and enhanced when ADA was added to cultures but remained lower in HIV patients than in healthy individuals. Increase in ADA costimulation is associated with lower HIV viral load and higher $CD4^+$ T cell counts. It is worth noting that, in patients under antiretroviral therapy, T cell proliferation is positively correlated with $CD4^+$ T cell count nadir, showing that ADA response is affected by preceding depletion of CD4+ T cells [113].

The occurrence of senescence age markers in HIV-infected individuals has suggested that these individuals might age prematurely or develop age-related diseases earlier in life [7, 114]. Some of the markers that indicate a senescent phenotype are the loss of CD28 costimulatory molecule, inverted CD4:CD8 ratio, an increase in IL-6 e TNF-α, and a decrease of IL-2 production by T cells as well as decreased telomerase activity [7, 84, 86]. Expression of ADA in $CD8^+CD28^+$ T cells boosts telomerase activity, counteracting the effects of adenosine in promoting replicative senescence [84]. ADA expression is negatively correlated with $CD8^+$ T activation markers and may help to monitor immune recovery, disease progression, or even age-related diseases in HIV-infected individuals. Activated $CD8^+$ T cells show downregulation of ADA expression in HIV infection, which may be a sign of poor immune restoration. In conclusion, ADA is an emerging biomarker of senescence in HIV-positive individuals [86].

HIV infection disturbs CD26/ADA costimulation, highjacks the immunomodulatory actions of Treg cells, and stimulates the generation of adenosine [108], in addition to downregulate ADA expression in lymphocytes [86]. In contrast, ADA enzymatic activity is reportedly increased in serum [103, 104, 115–120] and plasma of HIV patients [121–123] to overcome the effects of excessive adenosine levels.

ADA activity in HIV patients has long been evaluated in serum and plasma [121–123] lymphocytes [124], erythrocytes [125, 126], and platelets [71]. Correlations between ADA activity and several clinical parameters such as seroconversion [121, 126], prognosis [84, 97–100, 104, 107], immune activation [118], $CD4^+$ T cell count [115, 118–120, 123], viral load [118], CD4/CD8 ratio [119], coinfection [115, 120], and treatment outcome [71, 117, 119, 123] are discussed. Most of these studies aimed to use ADA activity as a biomarker but also helped to understand the pathological processes involved in the infection.

During seroconversion, ADA activity significantly increases in the plasma of HIV-infected patients [121, 122], but the correlation with disease progression had controversial findings. One study has found no changes between symptomatic and asymptomatic patients [121], while a more recent study found that ADA activity is incremented in symptomatic individuals [123]. Differences between these findings are certainly due to the use of different methodologies and the variances on the comparison parameters of disease progression. While the first one compared ADA activity with markers of activation, such as β2-microglobulin and neopterin [121], the second relied on a more established marker for prognosis, the $CD4^+$ T cell counts [123]. A third study compared $CD4^+$ T cell counts with β2-microglobulin and ADA activity, where a positive correlation was observed between ADA activity and β2-microglobulin levels as well as a negative correlation between ADA activity and $CD4^+$ T cell counts [115].

Several studies reported an inverse correlation between ADA activity and $CD4^+$ T cell counts in plasma [123] and in serum [115, 118–120]. Viral replication also influences ADA activity in serum as it increases with levels of plasma viral

load [118]. The CD4/CD8 ratio, an immune recovery and senescence marker, inversely correlates with ADA activity in serum [119]. Increased ADA activity in serum is also associated with an increase in activation markers such as CD14, a marker of monocyte activation and CD38, a marker of $CD8^+$ T cell activation [118].

No significant changes in serum ADA activity were observed when HIV-infected and HIV/tuberculosis-coinfected patients were compared [115]. However, when HIV-infected patients coinfected with hepatitis B or C were compared with HIV-monoinfected patients, the coinfected groups showed significantly higher serum ADA activities [120].

In treated HIV-infected patients, serum and plasma ADA activity levels remain elevated although in a lesser extent [117, 119, 123]. This may be explained by coinfections, antiretroviral toxicity, or simply by the persistent inflammation and immune activation triggered by residual viral replication present even when treatment is successful. Enduring inflammation and immune activation are a topic of utmost clinical importance since they are related to the development of non-AIDS-related diseases and premature aging [8, 127, 128].

Overall, ADA activity in serum and plasma are not specific biomarkers for individual alterations characteristic of HIV disease. Nevertheless, correlation between ADA activity and classical biomarkers used to monitor HIV infection, such as $CD4^+$ T cell counts and viral load, and association with activation markers and CD4:CD8 ratio, is evidence of ADA involvement in every aspect of HIV pathogenesis.

Concluding remarks

HIV infection represents a major challenge for public health, despite all the advances in this area of research. Understanding the pathogenesis of this infection has helped with the development of antiretroviral therapy, as well as with the search for a vaccine and a cure for HIV. Metabolic pathways, such as purine metabolism, play a great part in the immunopathogenesis of HIV [129].

We reviewed the immunopathogenesis of HIV and the role of adenosine and ADA in modulating the immune response to HIV. As part of the purine metabolism, we emphasize the importance of the adenosine pathway in several pathogenic mechanisms used by HIV to impair the host immune response. By counteracting the negative effects of overexposure to adenosine, ADA regulates the response to HIV to restore immune function. Given that ADA is a well-known marker of inflammation and that ADA activity correlates with $CD4^+$ T cell counts and activation markers in HIV infection, we highlight the connection between ADA function and every aspect of the immunopathogenic triad of HIV infection.

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Compliance with ethical standards

Conflicts of interest Daniela F. Passos declares that she has no conflict of interest.
Viviane M. Bernardes declares that she has no conflict of interest.
Jean L. G. da Silva declares that she has no conflict of interest.
Maria R. C. Schetinger declares that she has no conflict of interest.
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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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