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Immune Responses to Retroviruses

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Abstract (150 word max)

Retroviruses are genome invaders that have shared a long history of co-evolution with vertebrates and their immune system. Found endogenously in genomes as traces of past invasions, retroviruses are also considerable threats to human health when they exist as exogenous viruses such as the human immunodeficiency virus (HIV). The immune response to retroviruses is engaged by germ-line encoded sensors of innate immunity that recognize viral components and damage induced by the infection. This response develops with the induction of antiviral effectors and launching of the clonal adaptive immune response that can contribute to protective immunity. However, retroviruses efficiently evade the immune response due to their rapid evolution. The failure of specialized immune cells to respond, a form of neglect, may also contribute to inadequate antiretroviral immune responses. Here, we discuss the mechanisms by which immune responses to retroviruses are mounted at the molecular, cellular and host levels. We also discuss how intrinsic, innate and adaptive immunity may cooperate or conflict during the generation of immune responses.

Keywords

retroviruses, HIV, pathogen recognition, innate immunity, protective immunity, pathogenesis

1. INTRODUCTION

Retroviruses are characterized by their need for integration into the host genome to ensure their replication. They can exist both as exogenous viral particles with an RNA genome and as endogenous DNA elements. This dimorphic nature relies on the successful orchestration of the early phase of viral replication up to integration, including the dominant role of viral tropism for target cells, followed by the late phases of viral particles that produce viral progeny. These different phases produce many opportunities for interactions with the immune system.

At the cellular level, tropism determines the cells that will be affected and manipulated by viral replication. It defines the cellular source the infection utilizes to produce viral progeny, disseminate within the host and transmit the infection. It also defines the sets of cells that can directly engage with retroviruses via molecular interactions that contribute to the immune response. Importantly, the infected cells that produce the bulk of viremia are not necessarily equipped with the machinery to activate immune responses. Other specialized immune cells that have a minor contribution to viremia may be more significant to induction and control of the immune response.

Our understanding of immune responses to retroviruses relies in large on distinct historical studies that have defined the molecular replication of retroviruses or have dissected the principles, compositions and functions of the immune system in mammals. Recent studies benefited from this body of knowledge to define mechanisms and principles that determine the immune responses to retroviruses. Here, focusing mainly on lentiviruses, we review this emerging field of research, which operates at various levels in space and time – cells, host, evolution. We highlight the importance of these aspects in protection and pathogenesis, and we discuss emerging concepts.

2. THE INTRACELLULAR IMMUNE RESPONSE TO RETROVIRUSES

Before triggering of the adaptive immunity that recognizes infected cells, the innate immune system initiates responses through germ-line encoded factors. These responses are induced either by incoming viral particles or by infected cells.

1.1. Impact of restriction factors on immunity

The primary function of restriction factors is to directly inhibit viral replication, but their privileged interaction with retroviruses allows them to further participate to immune responses in some cases. For example, human cells expressing TRIM5 can induce a cytokine response when they are infected with murine or simian retroviruses, which could potentially contribute to the immune response during zoonosis (1). However, in dendritic cells, which are specialized in pathogen detection leading to the induction of immune responses, TRIM5 is SUMOylated, which disables its restrictive capacity while favoring an independent ability to promote the function of innate immune sensors (2). Tetherin, a restriction factor that mediates retention of retroviral particles when they bud from the cell surface, is able to initiate an inflammatory cytokine response (3). APOBEC3G and other restriction factors also contribute to shaping the immune response, and this has been extensively reviewed elsewhere (4). These interactions between restriction factors and the immune system often result in a transient enhancement in the expression of inflammatory cytokines by infected cells. The significance of restriction factors-induced cytokine responses to the overall immune response to retroviruses is not yet known.

1.2. The cellular immune response to retroviruses: Multi-faceted interactions of retroviruses with pathogen recognition receptors

The immune system can respond to retroviruses that exist in various states: extracellular viral particles, intracellular viruses and endogenous genetic elements. Immune cells can respond to retroviruses in these different forms by detecting specific viral elements (5) and through specialized cells (6).

In contrast to restriction factors, the primary function of pathogen recognition receptors (or sensors) of innate immunity is to induce an immune response following interaction with retroviruses. In professional antigen-presenting cells, the activation of innate immune sensors following pathogen recognition is particularly significant because it induces upregulation of MHC molecules, co-stimulatory molecule expression and other signals that enables activation of naïve T cells and their differentiation. Importantly, inflammatory cytokines cannot substitute for contact with pathogen components, indicating that pathogen recognition by innate sensors is essential to drive an immune response of sufficient quality (7).

1.2.1. The response to incoming viral particles

Retroviral particles contain an RNA that can function as ligand for TLR7 and TLR8 (8). In humans, TLR7 is best known for its expression on plasmacytoid dendritic cells (pDCs). pDCs express the HIV receptors and respond to viral particles by producing copious amounts of type I interferon. A study of SIV infection of rhesus macaques revealed that pDCs are not numerous in the first two weeks of infection at mucosal sites (9). They are thus not ideally positioned to induce a sufficiently fast antiviral response to suppress early viral spread. In the later stages of infection, the role of pDCs in responding to HIV remains incompletely understood. The hallmark of their activation is the production of type I interferon, which, although abundantly produced by pDC, can be produced by virtually any cell type that respond to a virus (10). In model systems, pDCs have an important role in modulating the response of dendritic cells, NK cells and T cells in lymph nodes (LN) (11) (12), which are interesting scenarios to examine in retroviral infection. pDCs exposed to HIV-1 also upregulate TRAIL (13) which could contribute to immunomodulation.

Myeloid (conventional) dendritic cells are constitutively present at mucosal sites, where they patrol and sample the environment, including the lumen (14). The two main subsets of myeloid dendritic cells, CD141+ DCs (DC1) and CD1c+ DCs (DC2) express both TLR7 and TLR8 at the protein level (15). CD141+ DCs are largely resistant to HIV-1 or HIV-2 infection and respond to viral particles in a TLR-dependent manner. Similarly, in CD1c+ DCs, HIV-1 does not replicate efficiently either and also elicits a TLR-dependent cytokine response. In contrast, HIV-2 efficiently infects CD1c+ DCs, and the TLR-dependent response is complemented by a response to the replicating virus. In mice, the TLR7 response to murine leukemia virus infection is essential for controlling viral replication, IgM and IL-10 production during the acute phase of viral infection (16, 17).

DC-SIGN interacts with mannose residues on the HIV envelope glycoprotein (18). Using MDDCs as model, this interaction has been proposed to participate to multiple signaling events that could contribute positively or negatively to the cellular immune responses. These include inflammatory cytokine transcription that depends on the positive activation of NF- κ B, in synergy with TLR4 (19), presentation of antigens from viral particles to CD8 T cells (20), but also downregulation of DC activation genes (21, 22) and evasion of MAVS-dependent innate immune signaling (23). The relative significance of these events to the overall immune response are not well understood.

The fusion of retroviral particles with the target cell membranes transforms the viral particles into intracellular components. The process of HIV entry into macrophages was found to induce a low-level type I interferon responses (24). This does not require viral nucleic acids and may result from sensing of the fusion event between the viral and cellular membrane. This mechanism has not been reported in other cell types.

1.2.2. The response to retroviruses in infected cells

1.2.2.1. The response to viral RNA

After entry, the viral RNA is delivered into the cytosol. Several viral RNA sensors have been described: RIG-I, MDA5, PKR, OAS1-3. Since cellular RNAs are abundant in the cytoplasm, these sensors rely on the recognition of specific chemical features of viral RNA to ensure specific detection. In the case of retroviruses, the RNA contained in viral capsids is a messenger RNA inherited from the previous infected cells. Its chemical nature is presumably indistinguishable from cellular RNA. Accordingly, no RNA-dependent type I interferon response in macrophages, dendritic cells or T cells infected with HIV has been reported after

viral entry before reverse transcription (25-27). The cellular response can also occur in response to viral RNA produced by transcription after integration. In dendritic cells, abortive viral RNA has been reported to activate a DDX3-MAVS signaling pathway, but HIV-1 appears to evade this pathway through an additional activity of DC-SIGN (23).

1.2.2.2. *The response to reverse-transcribed viral DNA*

Next to viral RNA, various responses are generated by recognition of the viral DNA produced as a result of reverse transcription. Upon infection of T cells isolated from lymphoid organs, the generation of abortive reverse transcribed dsDNA products activates the inflammasome, leading to release of the hallmark cytokine IL-1 β from infected cells and induction of pyroptotic cell death (28, 29). This mechanism could contribute to the characteristic depletion of CD4⁺ T cells observed in HIV patients. An important question is to understand how this mechanism impacts the dynamics of CD4⁺ T cell depletion (30). In particular, the relative depletion of productively infected vs. abortively infected vs. non-infected bystander cells deserves further study. How the HIV DNA activates the inflammasome is also incompletely understood. Unlike tonsillar T cells, T cells from blood are unable to mount this response (31). The dsDNA-binding protein IFI16 was proposed to function as a sensor linking HIV DNA to the inflammasome (32). However, IFI16 was not initially considered a DNA sensor due to its nuclear localization (33) and appears to function also as a transcription factor (34). It will be necessary to obtain genetic-deletion evidence and a detailed biochemical mechanism to understand more firmly the role played by IFI16 in this process (35). Similar to the inflammasome, whether HIV infection of primary T cells induces a type I interferon response has not reached a consensus: while some studies have reported a lack of induction in the presence of positive controls (25, 27, 36), more recent work suggests that type I interferon may be induced in certain experimental conditions (37). It is unclear however if the type I interferon response results from a direct recognition of viral components, or is a secondary, indirect response to changes in host cell physiology that may not be specific to the retroviral infection.

In macrophages, a low-level type I interferon is induced as a result of reverse transcription (24) but the bulk of the viral dsDNA appears to be cloaked from DNA sensors (26). Uncloaking of the viral DNA through capsid mutation or chemical inhibition of Cyclophilin A increases the type I interferon response. The underlying viral DNA sensor is not currently established, although the sensor of cytosolic DNA cyclic GMP-AMP synthase (cGAS) is suspected because the second messenger cGAMP, product of cGAS, was detected in these conditions.

In DCs, reverse transcription is heavily restricted by the dNTP hydrolase SAMHD1. A low fraction of DCs can be infected in vitro in the presence of SAMHD1 (22), and a fraction of infected DCs can be detected in the spleen of HIV-1-infected patients (38). However, DCs appear to not respond to, or neglect, the virus and do not get activated in response to infection; meanwhile the infection enables the virus to induce an immunosuppressive state in the infected DCs (22, 39). Alleviation of SAMHD1 enables DCs to get readily infected by HIV-1, revealing their ability to detect HIV-1 and to respond to it through innate immune activation (25, 40). The viral DNA is essential, but not sufficient, for recognition through cGAS (41). The ability of DCs to induce an innate immune response against HIV-1 when SAMHD1 restriction is alleviated has been independently reproduced in several studies (42) (43) (2, 44-47), and also confirmed in a mouse model of SAMHD1 deficiency (48). In contrast to HIV-1, HIV-2 encodes Vpx that degrades SAMHD1 and activates cGAS in MDDCs and CD1c⁺ DCs (15, 41). A majority of HIV-2 infected patients naturally control

viral replication and present immune characteristics that would be desirable in HIV-1 infection (reviewed in (49, 50)). HIV-2 infection also appears to provide partial cross-protection against HIV-1 in dually infected individuals (51). Infection and innate immune activation of DCs by HIV-2 may thus contribute to induction of this apparently protective immune response. Additional molecular differences between HIV-1 and HIV-2 may also contribute to their striking difference in pathogenesis (52)(53). Furthermore, SIVmac encodes Vpx and can counteract SAMHD1, but it causes a highly pathogenic infection that is generally not controlled by the immune response – hence the ability to degrade SAMHD1 is not sufficient to induce immune control of retroviruses. Infection and innate immune activation of DCs are regulated by a number of factors besides Vpx, including viral entry and the interaction between viral capsids and co-factors (15, 25, 26). It will be important to determine the ability of SIVs to infect and activate innate immunity in DCs of their respective host species, and to examine the role of simian host factors in these processes.

In cell lines that are not primary target cells, innate sensing of retroviruses can be observed. While these cellular systems enable fine molecular dissection, their relevance to the immune response in primary viral target cells is unclear. Importantly, the modalities of viral replication are closely associated with the metabolism of host cell replication, which is profoundly dysregulated in immortalized or transformed cell lines. For example, cGAS is required for the response to retroviral DNA of HIV, SIV and MLV in cell lines (43). In the case of HIV-1, this response is detected in the absence of viral integration in monocytic THP-1 cancer cells, which does not occur in macrophages or dendritic cells derived from primary cells (25, 43).

Important questions remain. To what extent the pool of viral cDNA recognized by sensors overlaps with the pool of integration-competent viral cDNA is not known. The intracellular location of reverse transcription and capsid uncoating with respect to these pools is also debated (54). The lack of consensus regarding these points can be attributed in part to historical data generated in transformed cancer cells instead of the relevant primary viral target cells, and to the fragility of the viral capsid structure that does not tolerate extensive genetic or biochemical manipulation. In macrophages derived from primary cells, the viral capsid protein clearly reaches the nucleus interior as a result of infection (55), supporting the idea that irrespective of whether it initiates capsid uncoating in the cytosol or at the nuclear envelope, the viral dsDNA remains associated with capsid proteins in the nuclear interior. The nature of the interactions that associate the viral capsid with the reverse transcribed DNA is not known.

2. THE HOST IMMUNE RESPONSE TO RETROVIRUSES

2.1. Induction of early innate immune responses against retroviruses at sites of transmission

Innate immune responses are induced in hosts early after transmission. Since retroviruses are generally transmitted by cellular fluids, these responses have been best described at mucosal sites. In SIV models, a hallmark of mucosal infection is the associated with increased numbers of pDCs, cytokines and chemokines (9, 56, 57). The timing of this increase varies from one to several days post-infection in these studies, indicating that these observed events may be highly dependent on experiment conditions. Collectively, these events nonetheless highlight an environment that favors the recruitment of immune cells early after retroviral transmission. The molecular events that contribute to these signals could originate from

multiple sources. Viral replication in target cells can lead to production of danger signals from compromised or dying infected cells, for example in the case of HIV replication in mucosal CD4⁺ T cells (58). Innate immune sensors can also recognize viral components from extracellular or intracellular particles, leading to the production of innate immune signals. The sequence of these molecular events when they occur in the context of tissues is not well understood. A hallmark of retroviral replication in tissues is the rapid induction of genes involved in innate immune signaling and inflammation (59, 60). These studies reported variable expression of genes belonging to the interferon pathway or the inflammasome pathway. This may be related to variable negative feedback of type I interferon on inflammasome activation (61-63). An additional important aspect of the mucosal immune response to retroviruses is the presence of the microbiota which could participate to the response. In the case of MMTV, virus-bound bacterial LPS activated TLR4 leading to production of IL-6 and IL-10 (64). While IL-6 is inflammatory, the induction of IL-10 could contribute to immune evasion by the virus.

2.2. The innate immune responses against retroviruses in lymphoid organs

Multiple paths can lead to induction of an immune response against retroviruses in lymph nodes. Intact viral particles can diffuse through the lymph and reach lymph nodes. At the lymph node, subcapsular macrophages were shown to capture MLV and HIV particles through SIGLEC-1, which can interact with lipids present at the surface of retroviral particles (65), and transmit viral particles to the interior of the node. DCs can also capture intact HIV particles in peripheral tissues and can in principle transport the virus to lymph nodes, although this has not been demonstrated directly *in vivo*. DCs have multiple mechanisms to capture and transport HIV. Immature MDDCs have a cytoskeleton-based machinery to capture HIV-1 particles and transmit them to T cells (66). Whether this process relies on a protein receptor at the surface of immature MDDCs remains unresolved. MDDCs that are treated with type I IFN express SIGLEC-1, which can also capture viral particles and contribute to T cell infection (67). Interestingly, SIGLEC-1 is also expressed on circulating blood monocytes from HIV-1 infected patients with elevated viral loads, presumably as a result of chronically elevated levels type I IFN interferon (68). MDDCs also express DC-SIGN which can interact with the envelope glycoprotein of HIV, however the role of this interaction in HIV capture and transmission to T cells in the context of dendritic cells varies between studies (69-72). Collectively, these events can contribute to the initial seeding of virus-infected lymphocytes within the lymph node. Incoming infected cells may also contribute to arrival of retroviruses in lymph nodes. In HIV-1 infection, the first infected cells that may reach the lymph nodes from tissues can also be DCs (73). This is presumably a rare event for HIV-1 due to restriction of DC infection by SAMHD1.

In SIV models, viral replication in lymph nodes induces a rapid type I interferon response in both pathogenic and non-pathogenic conditions (59, 74). This innate immune response is rapidly resolved in non-pathogenic conditions and maintained in pathogenic conditions. However, it is not known if the unchecked type I interferon response is the result of insufficiently controlled viral replication, or conversely whether it contributes to the lack of control (75). Importantly, studies in mouse models have revealed that the development of the antiviral immune response in lymph nodes is tightly orchestrated in both space and time. The induction of effective antiviral CD8⁺ T cell responses requires a CD4⁺ T cell response. Using HSV-1 and Vaccinia models, live imaging studies revealed that the initial activation of CD4⁺ T and CD8⁺ T cells is mediated by migrating DCs that are located in distinct regions. Later, distinct clusters of cross-presenting XCR1⁺ DCs (related to blood CD141⁺ DCs) interact with

both CD4⁺ and CD8⁺ T cells (76, 77). In a Vaccinia model, for this latter process, pDCs and the type I interferon signals that they produce are required to maximize activation of XCR1⁺ DCs and proliferation of CD8⁺ T cells (12). In the HSV-1 model, type I interferon signals are required to promote IL-15 secretion by DCs that is required for CD8⁺ T cell priming, in cooperation with CD4⁺ T cell-derived signals (78). How these mechanisms develop during the immune response to retroviruses is not yet known. They strongly suggest that the role of type I interferon cannot be inferred by studies that consider strength and duration of IFN signals in a bulk complex tissue such as the lymph node. It will be critical to reveal localized IFN-dependent signals and the intercellular mechanisms of communication that are required to prime effective anti-retroviral immunity.

2.3. Induction of host adaptive immune response against retroviruses

2.3.1. The T cell response in HIV and SIV infections

2.3.1.1. Induction of the CD8⁺ T cell response

HIV-1 and SIV induce massive activation of CD8⁺ T cells that can be detected after the eclipse phase of infection. This activation has been linked to expansion of HIV/SIV-specific CD8⁺ T cells but also of other antigen-specific cells due to bystander activation or transient reactivation of other chronic infections (79-81). However, recent studies on HIV-1-infected individuals during the period preceding or at the peak of viremia suggest that most of the CD8⁺ T cell expansion observed during this period (up to 80%) is indeed due to HIV-specific cells (82, 83). Over the last thirty years, numerous reports have shown that this robust CD8⁺ T cell response contributes to shaping the natural course of HIV and SIV infections (review in (84)). The development of HIV/SIV specific CD8⁺ T cells coincides with the decline of viremia (85) and has been shown to influence the viral set point (82, 86) and the seeding of reservoirs (83). Furthermore, there is a large body of evidence describing *in vivo* viral evolution to escape the pressure exerted by these responses even at the cost of some replication fitness (87). *De novo* responses are quickly generated against subdominant viral variants (87, 88), showing the ability of the immune system to develop robust CD8 T cell responses. Nevertheless, HIV-1 and SIV specific responses are ultimately inefficient to control infection, and exhaustion of CD8⁺ T cells (**Sidebar**), loss of proliferation, cytotoxic capacity and production of cytokines are commonly observed during chronic HIV-1 and SIV infection (84). Prolonged antiretroviral treatment does not, or only partially improves functionality of CD8⁺ T cells suggesting that some of the defects are imprinted in the T cell program (89). Moreover, early “protection” of the CD8⁺ T cell response by prompt initiation of antiretroviral treatment does not allow to infection control if treatment is interrupted (90), except in a few cases in whom the CD8⁺ T cell response does not appear to be decisive (91, 92). Overall, CD8⁺ T cells generated in response to HIV-1 and SIV seem to have limited antiviral capacity and further accumulate defects as a consequence of incomplete control of infection. Studies in mouse models have revealed that exhausted CD8⁺ T cells can be viewed as a distinct subset of CD8⁺ T cells, on the basis of defined epigenetic landscapes (93). Exhaustion of CD8⁺ T cells in HIV-1 infection may thus result from a specific differentiation program engaged early on during infection, and not necessarily from time-dependent decrease in functional capacities within central memory and effector cell subsets.

2.3.1.2. Functional properties of CD8⁺ T cells

It is still unclear which are the key characteristics lacking in specific CD8⁺ T cells generated during acute infection of most HIV-1 infected individuals. Early HIV-specific CD8⁺ T cells show delayed maturation and memory CD8⁺ T cell subsets with limited cytotoxic potential or antiviral activity are predominantly observed during the earliest phases of infection (79, 83, 94-96). When HIV/SIV-specific effector CD8⁺ T cells are generated, these cells are driven

towards senescence or exhaustion, lack expression of Bcl2 and CD127, exhibit increased mitochondrial dysfunction and are prone to apoptosis (81-83, 97, 98). Some individuals, known as HIV controllers, are able to naturally control infection to undetectable levels and are characterized by CD8+ T cells with peculiar properties (99). When compared to other HIV-infected individuals, HIV controllers show a higher frequency of fully differentiated CD8+ T cells (100, 101), expression of CD127 (102), increased survival capacity (103), and higher granule content and cytotoxic potential (102, 104), which ultimately results in their efficient capacity to counter infection through the elimination of infected CD4+ T cells (101). Natural control of HIV-1 infection has been linked to the selection of CD8+ T cells with particular TCR clonotypes that might ensure earlier recognition of infected cells, better antigen sensitivity and cross-reactivity or limit viral evolution by targeting epitopes within critical structural viral domains (84). A favorable genetic background might provide an influential advantage to achieve and/or maintain control of infection, in yet ill-defined circumstances, but it is not an essential factor for the development of efficient CD8+ T cell responses. For instance, natural control of infection is a relatively frequent phenomenon among HIV-2 infected individuals unrelated to their MHC background (105-107). Interestingly, CD8+ T cell responses found in HIV-2 controllers share part of the phenotypical and functional characteristics found among HIV-1 controllers and in particular strong specific antiviral activity (105). Some viral infections such as EBV or CMV generate potent and efficient CD8+ T cell responses characterized by the presence of a large proportion of CD27- effector cells (79, 80, 108). However, enhanced cytotoxic potential can be found among different subsets of EBV-specific memory CD8+ T cells (109) suggesting that functional properties of CD8+ T cells would not only be linked to their “classic” differentiation state or expression of effector molecules but also to a combination of properties including the relative expression of some transcription (such as t-bet or eomes) and survival factors (Bcl2 and CD127)(110-114).

2.3.1.3. Maturation of the CD8+ T cell response

The reasons explaining why the immune system generally fails to develop optimal CD8+ T cells against HIV or SIV infection remain elusive but this could be related to inadequate maturation of the T cell response. Precursor naïve CD8+ T cells can give rise to either effector or memory offspring (115, 116) and their fate appears determined by the threshold, duration and quality of the signal received through the TCR during priming and to environmental factors (117-119). Initial expansion of CD8+ T cells during acute infections is characterized by the release of short-lived polyclonal effector CD8+ T cells with low TCR affinity, while more potent cells with enhanced peptide sensitivity are found later during infection (120-122). In the context of HIV infection, the CD8+ T cell response also evolves but it is narrow during acute infection and becomes broader later, likely due to the recognition of multiple new variants (84, 87). Antigen sensitivity of HIV-specific CD8+ T cells also appears to decline with disease progression (123) but remains elevated in individuals who naturally control infection (124, 125). T cell affinity maturation (121) is proposed to occur through successive phases of interaction of CD8+ T cells with antigen presenting cells, with high affinity cells remaining longer in lymph nodes receiving further optimal activation signals (126). Local inflammation plays a critical role during this maturation process and influences the fate and the quality of CD8+ T cells as memory or effector cells (118, 126-128). HIV-1 and pathogenic SIV infections are characterized by massive viral replication in the lymph nodes and a very early and intense elevation of pro-inflammatory factors (129-133). The cytokine environment in the lymph node may skew the exposure to antigen necessary for the optimal maturation of the T cell response (127) and may drive the premature induction of immunosuppressive responses (134). The interactions of HIV-1 with DCs may

compromise optimal priming of T cells (see below). The presence of large numbers of target cells producing viral antigens in the lymph nodes may limit the re-localization of early primed CD8⁺ T cells and the interaction with DCs hence stopping their education (126). Activation of HIV-specific CD4⁺ T cells transforms them into privileged targets for HIV infection both in terms of susceptibility and proximity to replicating viruses (135), affecting their capacity to provide critical helper cues. Some of these circumstances may be attenuated among HIV-1 controllers resulting in a partial protection of the LN environment and favoring the maturation of optimal immune responses. For instance, dendritic cells from HIV-1 controllers produce limited amounts of pro-inflammatory cytokines (136) and the relative resistance of cells from HIV controllers to infection (137-139) may facilitate sensing of the virus by DCs (140), dampen the dynamics of viral replication in the LN and preserve CD4⁺ T helper cells (141).

2.3.1.4. *The CD4⁺ T cell response*

HIV-specific CD4⁺ T cells also expand during acute infection. The presence of HIV-specific CD4⁺ T cells with cytolytic or proliferative potential has been associated with lower levels of viremia (142, 143). The magnitude and the quality of the CD4⁺ T cell response has been linked to the efficiency of the CD8⁺ T cell response (144, 145). However, as for the case of CD8⁺ T cells, the functionality of HIV-specific CD4⁺ T cells is compromised and during infection they further lose critical properties such as capacity to proliferate or produce IL-2. As HIV-specific CD4⁺ T cells are preferential targets of infection (135) and are depleted during acute infection (146) it is unclear whether their poor quality is the result of deficient development or a characteristic of the cells that escape depletion. It is interesting to notice that HIV-specific CD4⁺ T cells share many of the characteristics of HIV-specific CD8⁺ T cells in HIV-2 infected individuals and HIV-controllers (147-149), suggesting that the optimal development of both compartments is intertwined and necessary for the efficient control of the infection.

2.3.2. *The T cell response in other retroviral infections*

In HTLV infection, clonal expansion of provirus-carrying CD8⁺ and CD4⁺ T cells occurs (150) while virus-specific CD8⁺ T cells are able to kill infected cells (151, 152), revealing a complex interplay between the infection and the immune response in the case of HTLV. The T cell responses to murine leukemia virus have been extensively reviewed elsewhere (153, 154). The T cell responses to other retroviruses has been minimally investigated.

2.3.3. *The B cell response to retroviruses*

The study of murine models of retroviral infection established that the antibody responses are essential for clearing retroviral infection (154, 155). IgM antibodies against HIV-1 are detected very early during acute infection but these antibodies do not possess neutralizing activities (156). Direct neutralization capacity depends on class switch and antibody affinity, which increases over several months of antigen exposure through B-cell maturation processes involving somatic hypermutation into Ig genes (157). However, the development of neutralizing antibodies appears delayed in HIV-1 infection when compared to other infections (156) and once developed these antibodies are not able to control HIV-1 infection due to the presence of multiple quasi-species and further capacity of the virus to adapt and escape neutralization (158). The antibodies adapt in turn to counteract the new variants. In rare individuals, this co-evolution of the virus and the antibody response results in the development of antibodies with very broad capacity to neutralize very distant variants (broadly neutralizing antibodies, bNabs) (158). Although the circumstances that lead to the development of these broadly neutralizing antibodies in a minority of the HIV-1 infected population remain unclear, high antigen exposure appears to be a major determinant as the

appearance of these antibodies is observed after several years of uncontrolled infection and/or in infected subjects with high levels of viremia (159). The rarity of this phenomenon appears to be related to the need to accumulate an extraordinary rate of mutations (160), 5-10 times higher than for other pathogens (161), to acquire HIV broadly neutralizing capacity.

As in the case of the T cell response, alterations in the secondary lymphoid organs provoked by HIV-1 infection may decisively alter the development of the antibody response. B cell dysfunction has been associated to the cytokine environment characteristic of HIV-1 infection and to cell exhaustion (162). In addition, follicular dendritic cells have been shown to trap and retain HIV-1 particles for very long time (163) and T follicular helper cells are a preferential target for HIV-1 replication (164, 165), critically sustaining HIV-1 replication in the LN. This may have several deleterious consequences, such as damaging the capacity of Tfh to assist antibody development or skewing the normal timing and localization of bNabs precursors within the LN due to continuous maintenance of strong antigen burden in the germinal centers (157). Besides direct neutralization, these problems can also affect the development of other antiviral activities mediated by antibodies such as antibody-dependent cell-mediated toxicity (ADCC) or antibody-dependent phagocytosis (158). Interestingly, enhanced ADCC capacity and polyfunctional antibody responses have been observed in HIV controllers (166, 167) and may contribute to the efficient viral control in these individuals. Antibodies from controllers appear to have higher functionality per molecule when compared to antibodies from non-controllers, suggesting qualitative differences (166). Further studies are needed to clarify if the antibodies found in HIV controllers are the result of optimal selection or may represent a set of antibodies with higher functionality that is lost during uncontrolled infection (168). Finally, the presence of mucosal HIV-specific IgA has been associated with protection from HIV-1 acquisition in rare highly exposed seronegative individuals (169), although the mechanisms leading to the development of these antibodies remain unknown.

2.4. Other immune responses to retroviruses

Although not expanded upon here, additional immune cells may participate in the immune response to retroviruses, including MAIT cells (170) and NK cells (171-173). Endogenous retroviruses or retroelements also elicit immune response in mice and humans (174, 175). At the cellular level, expression of retroelements can be induced by intracellular signaling and by epigenetic modulators, resulting in activation of innate immune signaling (176, 177).

2.5. The role of viral replication in dendritic cells during antiretroviral immune responses

DCs constitutively express the machinery to directly sense viruses. They also play an essential function in priming adaptive immunity. DCs are uniquely positioned to orchestrate the immune response to retroviruses and also to be hijacked by them.

2.5.1. Type I interferon regulates the immune response to retroviruses

Is sensing of viral particles and subsequent type I interferon production sufficient to induce a protective immune response to retroviruses? Isolated viral elements and viral particles are able to induce an immune response, for example through TLR7. However, while agonist-based TLR stimulation provides a potent adjuvant signal for vaccines, it is not known whether TLR-signals are sufficient to induce a protective immune response in the context of a natural viral infection. In HIV-1 infection, the production of type I interferon is consistent with the induction of TLR7-dependent responses, perhaps through pDCs, that fail to provide protective immunity. Abundant and potentially mislocalized production of type I interferon could contribute to desensitization of the type I IFN signaling pathway, to inflammation (75), to disabling the normal function of CD4⁺ and CD8⁺ T lymphocytes (178, 179) and to DC

depletion (180). In mice, IFN signaling desensitization is regulated by TAM receptor-mediated induction of a negative regulatory loop (181). It will be important to explore this pathway in HIV infection.

2.5.2. Retroviral infection of dendritic cells enables immune activation

Is retroviral replication in dendritic cells required to induce a protective immune response to retroviruses? It has been long inferred that viral infection of DCs participates to the immune response and host protection (182). Live attenuated viral vaccines often provide the most effective protection (183). However, viral infection leads to an irreversible demise of cellular integrity and enables manipulation of immune responses by the virus (184, 185). In HIV-1 infection for example, Nef expression in HIV-infected cells induces MHC-I downregulation from the cell surface, which results in a reduced ability to stimulate CD8⁺ T cells (186). Viral infection of DCs may also generate inflammatory mediators of the type that can contribute to disease (187). Thus, viral infection constitutes a paradox for DCs and it was postulated that all DCs may not be infected by viruses (188). As one solution to this paradox, it was recently found that the processes of viral infection and viral antigen presentation can be dissociated among DC subsets (15). CD1c⁺ DCs are efficiently infected by enveloped viruses such as HIV-2, influenza virus, VSV and HSV-1, at rates that are similar to cell lines used for viral titration. In contrast, CD141⁺ DCs are comparatively less susceptible to infection by these viruses and possess a constitutive mechanism of broad resistance at the level of viral fusion with the target cell membrane. This resistance is partial – it is not a restriction – but is nevertheless sufficient to restrain the damage (such as cell death) and immune manipulation (such as downregulation of the antigen presentation machinery from the cell surface) that would be induced as a result of viral infection. Co-culture experiments of CD141⁺ and CD1c⁺ DCs revealed a remarkable ability of CD141⁺ DCs to resist viral infection, while CD1c⁺ are simultaneously infected and produce viral antigens. In turn, CD141⁺ DCs that have acquired viral antigen from CD1c⁺ are able to present it by way of cross-presentation. Thus, infection of at least one subset of dendritic cells is likely one possible path to induce potent immune responses against retroviruses.

The ability of retroviruses to infect dendritic cells is highly variable between strains. MMTV infects dendritic cells and this contributes to the early events of viral transmission (189). In the case of HIV-1, the virus is potently restricted in DCs. Nonetheless, the virus is still able to infect a fraction of DCs in a single-round of infection at standard MOI. In the absence of an antiviral state, allowing viral multiplication and viral dissemination to ensue for multiple days may lead to an apparently high fraction of infected cells (39). In other words, while HIV-1 infection is restricted by SAMHD1, to what extent HIV-1 can replicate in DCs pertains to the differentiation and maturation state and experimental conditions (e.g. duration of the infection and differential survival of infected vs. non-infected cells). While a single-round infection will show a low fraction of infected cells, the virus will continue to replicate in a DC culture. In contrast to HIV-1, HIV-2 degrades SAMHD1 owing to the presence of Vpx. While initial studies suggested that bulk DCs cultures are poorly susceptible to HIV-2 infection (190), studies with sorted DCs show that CD1c⁺ DCs are readily infected by HIV-2 in a Vpx-dependent manner (15). Of note, MDCCs that are differentiated *in vitro* appear unable to mediate viral fusion and entry of HIV-2 particles (191), suggesting that while MDCCs recapitulate the downstream steps of HIV-2 infection and innate sensing (41), they do not faithfully recapitulate the HIV-2 viral entry observed in primary DCs (15) for reasons that have not yet been revealed.

2.5.3. Protective immune responses to retroviruses may be induced by DC infection–dependent and –independent paths

Is DC infection in the absence of SAMHD1 required for inducing an effective immune response to retroviral infection? In addition to enabling innate sensing and induction of a local antiviral state, infection of DCs in conditions where SAMHD1 is abrogated potentially enhances antigen presentation and activation of virus-specific T cells (25, 48), which are critical events during priming of the adaptive antiviral response. Enforced viral replication in myeloid cells as an immunological mechanism to promote effective immune responses has also been recently demonstrated in the case of another RNA virus, VSV (192). In HIV-1 elite controllers, increased accumulation of viral DNA products that can activate cGAS has been reported in DCs, but the susceptibility of the DCs to infection was simultaneously found to be decreased, indicating that these two events can also be dissociated (139, 140). One approach to address the role of DC infection in the control of HIV infection has been to monitor the role of the SAMHD1-degradating protein Vpx. However, in addition to its role in DC infection, Vpx plays a critical role in the infection of resting T cells (193). Indeed, a mutated Vpx allele was found in an aviremic HIV-2 patient (194) and infection of macaques with Vpx-deficient SIV greatly attenuated viremia and pathogenesis (195). Thus, addressing the role of DC infection in the induction of antiviral immunity to retroviruses will require the development of specific models that isolate this process from other confounding factors such as viral replication in T cells and viremia.

Importantly, protective immunity to retroviral infection can also be induced in the absence of DC infection. For example MLV is restricted by SAMHD1 (196) and DCs are generally considered terminally differentiated non-dividing cells which prevents nuclear entry of MLV, although evidence of DC proliferation have been observed in rare instances (197) (198). Despite this resistance of DCs to MLV infection, an efficient CD8⁺ T cell responses can be induced by MLV infection (199), and a protective antibody response can be also be activated by TLR signaling (200). Overall, this demonstrates that DC-infection independent paths also exist to induce protective immunity to retroviral infection (**Table 1**).

3. IMMUNE EVASION BEYOND VIRAL ESCAPE: NEGLECT BY IMMUNE CELLS

3.1. From viral escape to neglect by infected cells

In an infected host, the ability to control the replication of retroviruses requires a persistent recognition of viral components and of virus-infected cells to keep the infection in check, or sterilize it. Retroviruses have evolved a vast array of mechanisms to evade immune responses which has been reviewed in detail elsewhere (201). In an infected host, retroviruses show a remarkable ability to evade the adaptive immune response mediated by B cells, CD4⁺ and CD8⁺ T cells. This is enabled by their mechanism of replication that relies on an error-prone reverse transcriptase. The acquired immune responses also adapt as a result of viral evolution within a host, and new antiviral cellular clones emerge as a result of intra-host retroviral evolution. In addition, complex retroviruses also encode accessory proteins that manipulate the host infected cells, examples include Nef that downregulates Class I molecule expression at the surface of infected cells (186) or Env-mediated suppression of MAVS-dependent sensing in MDDCs (23). These mechanisms limit the ability of T cells to recognize and destroy infected cells. Retroviruses have also evolved counter-measures to neutralize host restriction factors, either by evolution of structural proteins (e.g. capsid evolution and TRIM5 restriction; envelope evolution and tetherin restriction) or dedicated accessory proteins (e.g.

Vpu for tetherin, Nef for SERINC, Vif for APOBEC3G). In addition to these well documented mechanisms of immune evasion, we propose that neglect of retroviruses by specialized immune cells also contributes to developing an immune response that may be quantitatively strong, but qualitatively insufficient to control viral replication (**Table 2**). In contrast to viral escape, neglect by host cells does not require viral-encoded activities.

3.2. Examples of neglect

A first example is the lack of HIV-1 recognition by cGAS in MDDCs and CD1c+ DCs. Most lentiviruses antagonize SAMHD1, and this ability preceded the birth of Vpx in lentiviruses (202). This enables efficient lentiviral replication in non-dividing cells such as macrophages, resting T cells and dendritic cells. In dendritic cells, innate immune activation of DCs by HIV-2 also requires the Vpx protein (15, 41). SIVcpz/HIV-1 lacks both Vpx and the ability to degrade SAMHD1 (202). The loss of this activity in SIVcpz/HIV-1 may be due to the benefit of escaping innate immune response in DCs, but it could also be due to an alternative adaptation in order to achieve sufficient replication in target cells and transmission. As a result of these different scenarios and of the dual role of SAMHD1 degradation in viral replication and innate immune recognition, there is currently no evidence that HIV-1 would have lost the ability to degrade SAMHD1 for the sole purpose of escaping innate immune recognition in DCs. In contrast, it is clear that human DCs lack the ability to respond to cytosolic HIV-1 through cGAS as these cells have a threshold for viral recognition that is not adapted to detect HIV-1. HIV-1 can infect a small fraction of DCs, but SAMHD1 considerably limits the extent of reverse transcription. On one hand, this limits the rate of DC infection as discussed above. On the other hand, this greatly limits the amount of viral DNA that is produced in the cells. While in theory only one copy of viral DNA per cell is sufficient to establish viral integration and viral expression, the response through cGAS is an enzymatic process that results from the concentration of viral DNA per cell (43, 203). In addition, the viral capsid of HIV-1 limits recognition of the viral DNA before viral integration, even when the latter is produced at sufficient concentrations (25, 26). Thus, the lack of cGAS response in human DCs should currently be considered a host neglect mechanism and not a viral escape mechanism.

A second example of neglect by the host is the latent integrated viral reservoir. In its integrated form and in the absence of viral protein expression, there is no evidence that immune cells are able to recognize the presence of virally-infected cells. Interestingly, circulating latently infected cells may express specific surface proteins, including CD32a (204). This implies that the immune system neglects the presence of the latently infected cells, despite the presence of a seemingly specific transcriptional and cell surface signature in the infected cells. This notion that latently infected cells are neglected despite the presence of integration viruses does not negate the idea that viral latency is a virally-induced mechanism in the first place.

A third example of neglect by the host is the paucity of virus-specific CD8+ T cells in germinal centers that contain productively infected CD4+ T_{FH} cells (205, 206). Within CD4+ T cells, CD4+ T_{FH} are a major compartment for viral replication (207). However, virus-specific CD8+ T cells require specific chemoattractant signals, such as the CXCR5-CXCL13 interaction, to reach sites of infection. Virus-specific CXCR5+ CD8 T cells are found in HIV-infected patients (206). A likely possibility to explain the lack of virus-specific CD8+ T cells in germinal centers is that the chemo-attracting signals are not sufficiently produced from these sites of viral replication. Overall, germinal center cells appear to neglect the presence of the virus, leading to seemingly insufficient amounts of chemoattractant for CD8+ T cells. This may prevent eradication of the viral infection, although it does not preclude immune control in the infected individual.

3.3. Neglect of retroviruses and host evolution

It is likely that the various mechanisms of neglect by immune cells would be selected against by hosts across evolutionary time, and that they can be observed today mainly in cases of recent zoonosis such as HIV-1 infection. Nevertheless, under what circumstances would neglecting retroviruses be a selective advantage? One possibility is that a certain level of retroviral neglect may be required to tolerate the presence of retroviral transposons that are an integral part of host genomes and are biologically active. For example, TREX1, which limits recognition of retroviruses, is required to limit autoinflammation and autoimmunity that is presumably mediated by the accumulation of retroviral retroelements (208). Another possibility is that raising the sensitivity of downstream signaling pathways required for sensing of retroviruses could lead to pathogenic signaling, such as that documented in several interferonopathies (209). Finally, it is also possible that the mechanisms capable of attending to retroviruses are competing with other essential mechanisms of host physiology or host-pathogen interactions, and that the fitness cost of monopolizing resources to allow retroviruses recognition at the expense of other processes may be too high. Irrespective of these mechanisms, a distinctive feature of host neglect is that the insufficient immune responses that result from this phenomenon do not require viral escape mutation or the expression of specifically encoded antagonistic viral factors, and thus represents a distinct principle of immune evasion.

4. COMPETITION BETWEEN IMMUNE RESPONSES: COOPERATION & CONFLICT IN ANTI-RETROVIRAL IMMUNE RESPONSES

The variety of distinct immune responses to retroviruses describe herein co-exist in a given host. In principle, they should cooperate in order to maximize viral control and host survival. However, they may individually generate immune conflict which may contribute to promoting viral replication and pathogenesis.

4.1. Cooperation in antiretroviral immune responses

The immune response to retroviruses involves three main mechanisms of viral recognition (**Figure 1A**). Intrinsic restriction factor and interferon-induced antiviral effectors directly interact with retroviruses or interferes with their enzymatic activities to block their replication. Innate immunity comprises viral recognition receptors that recognize virus-associated molecular patterns and pathogenesis patterns (210). Adaptive immune cells recognize viral epitope and protein conformations through presentation on MHC molecules and antibodies. In general, these three mechanisms cooperate through intercellular communications. They can also synergize at the molecular level, for example tetherin both directly limits viral budding and also signals through NF- κ B to produce inflammatory cytokines (211). In the case of retroviruses that rapidly evolve, these mechanisms can also cooperate through the selective pressures that they impose on viral replication. For example, a retrovirus that would rapidly evolve escape mutations that allow it to evade the CTL response may diminish its ability to escape recognition by antiviral effectors. This cooperation contributes to shaping the genotype landscape of retroviruses in hosts (**Figure 1B**) (212).

4.2. Conflict in antiretroviral immune responses

Conflict can also occur between immune responses to retroviral infection, or between mechanisms of viral replication and immunity. A first example is the dual role of SAMHD1 that functions as a restriction factor, but also limits the ability of DCs to detect retroviral DNA. For HIV-1, SAMHD1 limits the production of a viral burden through infection of resting CD4⁺ T cells which may benefit the host (213). However, innate immune recognition in DCs is also limited, which benefits the virus (25). HIV-2 encodes Vpx to degrade SAMHD1, contributing to the both viral burden in resting CD4⁺ T cells and innate immune activation in DCs. In terms of producing an effective antiviral response to HIV in humans, the reduced pathogenicity of HIV-2 suggests that favoring innate immune sensing at the cost of viral replication in other target cells provides a higher level of protection. Interestingly, this competition model was validated in a mouse model for SAMHD1 deficiency (48). A second example is the dual role of type I interferon that induces an antiviral cellular state, but whose persistent presence disrupts proper development of the adaptive T cell response (75, 178). Transmitted-founder viruses have a reduced susceptibility to the antiviral effect of type I interferon (214). This indicates that in acute viral infection, type I interferon signals likely contribute to limiting early viral replication. However, when chronic infection is established, chronic immune activation and chronic type I interferon production correlate with the gradual loss of immune control of viral replication. In animal models, inhibiting type I IFN signals in the chronic phase enhances viral replication, but also restores the development of virus-specific T cells (178, 215). The restoration of the antiviral T cell response may result from both increased viral antigens and suppression of inhibitory mechanisms on T cell functions. Thus, there is a conflict between the ability of type I IFN to suppress viral replication and its contribution to chronic inflammation that fosters immune dysfunction.

Overall, conflicts in the antiretroviral immune responses appear to result from the tropism of retroviruses for immune cells. This creates an intertwined system where the virus benefits from disabling immune circuits while the immune response benefits from enforced viral replication through viral detection and viral antigen synthesis.

5. CONCLUSIONS AND PERSPECTIVES

The multiple mechanisms by which immune responses are mounted against retroviruses emphasize that the immune system of mammals is well equipped to deal with these viruses. The mammalian immune system has the capability to control, and in some cases, sterilize retroviral infections. Multiple immune paths have the capacity to reach this goal. To this end, the virus-centric view that viral replication in cells would be systematically detrimental to the host should be reconsidered. Sufficient viral infection in specialized immune cells appears to be a general property of the vertebrate immune system that can initiate the path for the development of potent immune responses to viruses in general, and retroviruses in particular. Accordingly, the preferential tropism of retroviruses to immune cells and the multiple mechanisms of immune cell manipulation they encode could be viewed as a viral strategy to maximize control of the immune response. Intriguingly, preferential tropism of retroviruses to immune cells could have equally resulted from trapping retroviral replication within the immune system during evolution in order to achieve a sufficient level of immune response. The immune response to retroviruses is highly complex, with multiple routes, cooperation and conflicts between specialized immune cells. It is important that we understand not only how viruses have evolved and continue to evolve to escape immune control, but also how specialized immune cells can detect, control or neglect retroviruses. Understanding the mechanisms that permit effective antiretroviral immune responses in non-pathogenic conditions, which may take the form of local or systemic control, is thus critical if we aim to

learn the necessary knowledge to be able to restore such immune responses during pathogenic retroviral infection.

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Figure 1 Cooperation in antiretroviral immune responses.

(A) Three main mechanisms of viral recognition are implicated in the immune response to retroviruses.

(B) Retroviral genomes evolve on a landscape that is shaped by three main forces. Optimal genomes can replicate without trade-off. Under increased pressure from one mechanism, retroviral evolution can lead to increased susceptibility to the two other mechanisms, leading to a lethal trade-off. Adapted from (212).

Sidebar T cell exhaustion in viral infection

In HIV infection, the induction of chronic immune activation in CD8⁺ T cells correlates with the level of viremia (216). Studies in mouse models of chronic infection have revealed the existence of an "exhausted" CD8⁺ T cell state associated with chronic viral replication (217), which is also observed in HIV-1 infected patients and is associated with disease progression (218). Hence, while classically considered a consequence of the lack of control, CD8⁺ T cells exhaustion may actually result from initial priming events, perhaps pre-established, that may cause the lack immune control. CD8⁺ T cell exhaustion is a fascinating state of CD8⁺ T cells that likely underlies the inability of the immune system to control or eliminate retroviral infection, as in most HIV-1 infected individuals.

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