Myeloid-derived suppressor cells and the pathogenesis of human immunodeficiency virus infection

Mahmoud Mohammad Yaseen, Nizar Mohammad Abuharfeil and Homa Darmani

Department of Biotechnology and Genetic Engineering, Faculty of Science and Arts, Jordan University of Science and Technology, Irbid 22110, Jordan

There are several mechanisms by which human immunodeficiency virus (HIV) can mediate immune dysfunction and exhaustion during the course of infection. Chronic immune activation, after HIV infection, seems to be a key driving force of such unwanted consequences, which in turn worsens the pathological status. In such cases, the immune system is programmed to initiate responses that counteract unwanted immune activation, for example through the expansion of myeloid-derived suppressor cells (MDSCs). Although the expansion of immune suppressor cells in the setting of systemic chronic immune activation, in theory, is expected to contain immune activation, HIV infection is still associated with a remarkably high level of biomarkers of immune activation. Paradoxically, the expansion of immune suppressor cells during HIV infection can suppress potent anti-viral immune responses, which in turn contribute to viral persistence and disease progression. This indicates that HIV hijacks not only immune activation but also the immune regulatory responses to its advantage. In this work, we aim to pave the way to comprehend how such unwanted expansion of MDSCs could participate in the pathology of acute/primary and chronic HIV infection in humans, as well as simian immunodeficiency virus infection in rhesus macaques, according to the available literature.

1. Introduction

Both arms of the innate immune system—namely the cellular (monocytes/macrophages (Mo/MΦ), dendritic cells (DC), natural killer (NK) cells, basophils/mast cells, polymorphonuclear neutrophils (PMN), eosinophils and the newly identified innate-like cells including B1 and marginal zone B cells) and humoral (complement system) responses—play indispensable roles in: (i) recognizing/sensing and clearance of ‘cell-debris, foreign substances, and invading pathogens’; (ii) antigen internalization and presentation to shape the adaptive immune system activation; (iii) immune-activated downregulation (the so-called immune regulation) upon the clearance of pathogens and abnormal cells or during chronic immune activation; (iv) immune tolerance; (v) maintaining the architecture of tissues (so-called tissue remodelling); as well as (vi) newly emerging functions, in particular, immunological memory after reinfection [1–7]. Innate immune cells can sense both pathogen-associated molecular patterns (PAMPs) expressed by pathogenic and nonpathogenic microbes, and/or danger-associated molecular patterns (DAMPs) exhibited in stressed or damaged cells/tissues by different classes of receptors, the so-called pattern recognition receptors (PRRs) [8]. To our knowledge, PRRs can be categorized into five major classes of receptors: (i) toll-like receptors (TLRs), (ii) nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), (iii) C-type lectin receptors, (iv) retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and the recently...
Immune regulation is a highly sophisticated process that is orchestrated by different immune suppressor cell populations. Under normal physiological conditions, different immune cell populations that belong to the innate immune system (e.g. innate-suppressor cells of myeloid origin called myeloid-derived suppressor cells (MDSCs)) and/or the adaptive immune system (adaptive-suppressor cells including regulatory T (Treg) cells and regulatory B (Breg) cells) work together in harmony to terminate inflammation and revert back to the homeostatic state [6,7,17–19]. On the other hand, it is essential to keep in mind that although immunosuppressive cells could have a positive impact in the context of containing inflammation [20], especially if this is accomplished as soon as they become activated, failure to achieve such a goal could result in unwanted consequences, as seen in chronic inflammatory pathological conditions, such as observed in different types of cancer, certain autoimmune disorders and various infections [6,20]. In other words, prolonged activation of immune regulatory processes (i.e. chronic activation of immunoregulatory cells) results in the suppression of specific immune responses to a given immunopathological condition, thereby leading to disease persistence/progression (discussed below) [6,7].

In this paper, we will focus our discussion on the role of innate immune suppressor cells, namely MDSCs, in the pathogenesis of HIV infection alone. Therefore, the role of MDSCs in HIV patients co-infected with other pathogens such as cytomegalovirus, hepatitis C virus (HCV) or Mycobacterium tuberculosis, or suffering from other inflammatory pathological conditions, including cancer, will not be included in this work. It is important to note that understanding the biological properties of MDSCs in normal and abnormal conditions is necessary to understand the pathophysiology of human disease, and subsequently to develop new potential therapeutic strategies [6,7]. Hence, in order to clearly understand the following discussion of the role of MDSCs in HIV infection, we encourage readers to examine our recently published review articles on this topic [6,7].

Let us begin by reviewing the general properties of MDSCs. As potent immunoregulatory cells of myeloid origin (i.e. express myeloid markers), MDSCs comprise a mixture of mature and immature immune suppressor cell populations that mainly express either monocyteic or granulocytic features. As such, there are two main populations of MDSCs, namely monocytic-MDSCs (M-MDSCs) and granulocytic-MDSCs (G-MDSCs or PMN-MDSCs). Under normal physiological conditions, MDSCs are expanded as a result of inflammatory immune responses for the purpose of terminating the damaging effect of unwanted inflammatory responses and/or achieving immune tolerance, as seen during pregnancy and lactation [7]. On the other hand, under non-physiological pathological conditions, including cancer and infectious diseases, such as HCV and influenza virus infection, expansion of such cells could worsen the clinical status of these pathological conditions [6,7]. The role of MDSCs during HIV infection will be addressed in the following discussion.

2. The role of myeloid-derived suppressor cells in human immunodeficiency virus infection

HIV is a splendid example of a chronic infectious pathogen that successfully evades and invades the immune system

and mediates chronic immune activation [1,2]. Apart from the direct immunopathological effects mediated by the virus itself, chronic immune activation, upon HIV infection, leads to immune dysfunction and exhaustion, both of which contribute to disease progression and HIV persistence [1,2,21–23]. To counteract such chronic immune activation, the expansion of immunoregulatory cells during HIV infection is mediated [24,25]. It is essential to keep in mind that although immunoregulatory responses could play a role in preventing/limiting the cell/tissue damage mediated by chronic immune activation upon HIV infection, these immune responses could limit anti-HIV immune responses resulting in defective immune responses against this virus [24–28], and thus enhancing its persistence, as aforementioned. From this point of view, in the following sections, we will focus on the expansion of MDSCs and their pathological roles during the primary and chronic phases of HIV infection.

2.1. Myeloid-derived suppressor cells expansion during the course of human immunodeficiency virus and simian immunodeficiency virus infections

As previously stated, it is widely accepted that MDSCs are expanded in various pathological conditions including cancer, sepsis, autoimmune disorders, microbial infections and allergy, among others. This expansion is associated with suppressive immune responses that worsen the status of these pathological conditions, as detailed in our recently published reviews [6,7].

The story of MDSCs in HIV infection began when the following scenario was presented. During the course of HIV infection, most patients can partially control viremia for a certain time. Unfortunately, after a short time, this control is lost in most cases. To address whether MDSCs, as a potent immunosuppressive cell population, play a role in this event during HIV infection, in 2012 and for the first time in humans, Vollbrecht et al. [29] reported a significant increase in the frequency of MDSCs, particularly PMN-MDSCs, in chronically HIV-infected patients when compared to healthy subjects. They were also the first group to describe the positive association between the expansion of MDSCs and HIV disease progression. Indeed, this observation was documented upon comparing two HIV-infected populations in different clinical stages, namely HIV progressors (i.e. HIV patients with a viral load greater than 5 × 10⁴ copies per ml and CD4+ T-cell counts lower than 250 cells per µL) and HIV controllers (i.e. PMN-MDSCs, but not PMN-MDSCs, are dramatically elevated in seropositive chronic HIV-infected patients when compared to healthy subjects. One could ask why there is such difference in MDSC phenotypes, even within the same pathological condition; HIV infection in our case? The answer to this question lies in the fact that MDSCs are very sensitive to some manipulations, including the methods of sample processing. For example, cryopreservation can reduce the viability of MDSCs, in particular the PMN-MDSCs [7]. Therefore, it is rational to link this difference in MDSC phenotypes to the differences in sample processing between the two studies, especially since Qin et al. used cryopreserved samples. However, according to Qin et al., this is not the case because they repeated their experiments on the same HIV patients using fresh samples to exclude the possibility of sample processing being the underlying cause of such differences in MDSC phenotypes observed in their study and that of the Vollbrecht group [29]. Qin et al. suggested that this could be due to the difference in the systemic cytokine responses, as a consequence of the difference in HIV strains between patients. Another plausible explanation for this difference is the clinical stage of HIV infection. Generally, it is agreed that the inflammatory microenvironment plays a critical role in driving the differentiation and expansion of one MDSC population over the other [6,7]. In the context of HIV infection, as the clinical stage of HIV infection advances, immune depletion (mainly CD4+ T cells) and alteration in the inflammatory microenvironment become more observable. As such, we could refer the expansion of M-MDSCs over PMN-MDSCs in Qin group’s study, at least in part, to the clinical stage of enrolled patients. This is true, especially taking into account that HIV patients in the study of Vollbrecht et al. [29] were at a less advanced clinical stage than those in the study of Qin et al. In other words, most of the enrolled HIV patients (approx. 70%) in the study of Qin et al. were at the C3 clinical stage according to the USA CDC classification system (i.e. patients exhibited acquired immunodeficiency syndrome (AIDS) symptoms; CD4+ T cells greater than 200 per ml). However, other plausible explanations could also exist and will be discussed later. With respect to the impact of ART on the frequency of MDSCs, they have shown that despite the fact that the frequency of M-MDSCs were decreased after the initiation of HAART to a level below the baseline level, still the levels of M-MDSCs were significantly higher in HIV-infected patients compared to those in healthy subjects. This may indicate that even prolonged HAART fails to renormalize the levels of M-MDSCs. Their results have also strongly supported the direct correlation between the levels of M-MDSCs, but not PMN-MDSCs, and disease progression since M-MDSCs levels were directly associated with the viral load and indirectly with the CD4+ T-cell counts. Meanwhile, there were no differences in the frequency of PMN-MDSCs between HIV-infected patients and healthy individuals. Qin et al. also confirmed the direct link between HIV viremia and M-MDSC expansion,
since a dramatic decrease in plasma viremia coincided with a notable decrease in MDSC frequency. Furthermore, they showed that HIV-infected patients in advanced disease stages (less than 200 CD4+ T cells/µl) and especially those with AIDS symptoms had higher M-MDSC levels than those without AIDS symptoms.

Such inconsistency in results regarding which population of MDSCs (i.e. M-MDSCs or PMN-MDSCs) is expanded during the chronic phase of HIV infection still exists in later studies. For example, Bowers et al. [31], Tumino et al. [32] and Zhang et al. [33] confirmed the results of Vollbrecht et al. [29] in that PMN-MDSC populations become expanded over M-MDSC populations during the chronic phase of HIV infection. On the other hand, in accordance with the results of Qin et al. [30], Garg et al. [34] and Wang et al. [35] also demonstrated that M-MDSCs are expanded during chronic HIV infection. However, the study of Garg et al. [34] could not determine whether PMN-MDSCs are expanded or not, since the anti-CD14 (a marker for monocytic origin) but not anti-CD15 (a marker for granulocytic origin) antibody was used in their study. Therefore, it is not possible to exclude the likelihood of PMN-MDSC expansion, since the two populations could be equally expanded simultaneously within the same patient, or one population may be predominant over the other [36]. Furthermore, the total number of enrolled HIV patients (i.e. patient sample) in the study of Garg et al. [34] was too small, so the interpretation of the results cannot be generalized. However, since the in vitro findings that M-MDSCs are expanded upon exposure to infectious and non-infectious HIV particles, as well as upon exposure to gp120, were consistent with the in vivo results, this could strengthen the results of this study.

MDSCs are reported to be expanded in chronic inflammatory conditions including cancer [6,7]. The results of initial studies on HIV infections were in agreement with these studies, in that the expansion of MDSCs firstly confirmed during the chronic but not acute phase of HIV infection. However, later on, particularly in 2017, different groups of investigators confirmed that MDSCs are also expanded during the early/acute phase of HIV infection (also known as primary HIV infection) [33,37]. Of these groups, Tumino et al. [37] studied the kinetics of MDSC expansion from the acute to the chronic phase of HIV infection and determined the factors involved in such expansion. They compared the frequency of MDSCs in HIV patients in acute and chronic phases with healthy donors and observed that MDSCs, particularly PMN-MDSCs, are expanded very early, within the first weeks (particularly in Fiebig stages II/III) post-HIV infection and remained high over time. Zhang et al. [33] also investigated the alterations of MDSCs in primary HIV infection and their association with disease progression. They reported that MDSCs, particularly PMN-MDSCs, are expanded during both the primary and chronic phases of HIV infection when compared to healthy donors, and such expansion was shown to be associated with disease progression markers. Furthermore, according to their results, HIV replication did not seem to be involved in PMN-MDSC expansion during acute HIV infection. This is especially true, since there was no correlation between viral load and PMN-MDSC expansion in acutely infected HIV patients. Other groups, such as Grutzner et al. [38] and Agrati et al. [39], have also confirmed that MDSCs are expanded during the primary phase of HIV infection.

Using animal models, Dross et al. [40] were the first to study the kinetics of MDSC expansion in simian immunodeficiency virus (SIV)-infected rhesus macaques. Similar to what has been observed in the study of Tumino et al. [37], MDSC expansion was confirmed in the early phase of SIV infection and such expansion continued to the chronic phase. Moreover, Sui et al. [36] were the first to study the expansion and the tissue distribution of MDSCs during SIV infection in rhesus macaques. In agreement with previous results, Sui et al. [36] also confirmed that MDSCs are expanded in peripheral blood during the chronic phase of SIV infection. Paradoxically and unexpectedly, they observed that the level of MDSCs was decreased in the bone marrow of chronic SIV-infected rhesus macaques and such decreases were associated with disease progression markers. This observation was of a surprise because of the fact that, in all the previous studies on different inflammatory pathological conditions including cancer, once the expansion of MDSCs occurs, the distribution of such cells was almost consistent in different anatomical compartments including blood circulation and bone marrow, and such expansion was shown to be associated with disease progression [6,7]. It is worth mentioning that the results of Sui et al. [36] are very important and highly unexpected, thus, we are planning to address their results in a separated work.

Taken together, these findings clearly emphasize the expansion of MDSCs during the acute and chronic HIV and SIV infections and confirm that such expansion has a negative impact on the disease progression status. Therefore, in the next sections, we will address the pathological role played by MDSCs in a comprehensive manner in the hope of gaining a better understanding of the pathophysiology of HIV infection.

3. Myeloid-derived suppressor cell expansion and the pathogenesis of human immunodeficiency virus infection

The mechanisms of immune suppression and the pathological role played by MDSCs during different pathological conditions including cancer are relatively well established when compared to HIV infection. However, in recent years, great achievements in MDSC/HIV research field have been made. As such, in this section, we address this issue in a comprehensive manner and we have collected the available results on MDSC and HIV infection alone during the period from 2012 to the time of paper submission.

3.1. Myeloid-derived suppressor cells during chronic human immunodeficiency virus infection

Although MDSCs can suppress immune responses mediated by different types of immune cells including DCs, monocytes and NK cells, MDSCs mainly suppress immune responses mediated by T cells [6,7]. This is the main reason why studies on HIV infection focus on the suppressive role of MDSCs on T cells. Vollbrecht et al. [29] were the first to demonstrate the pathological role of MDSCs during the chronic phase of HIV infection. With respect to their immunosuppressive function,
it is essential to know that MDSCs can mediate their suppressive activity directly via engagement with other immune cells and/or indirectly via mediating the expansion of other immunosuppressor cells such as Tregs, or secreting immunosuppressive molecules (figure 1). To address this issue, Vollbrecht and colleagues incubated PMN-MDSCs with peripheral blood mononuclear cells (PBMC)-obtained from HIV controllers. Interestingly, PMN-MDSCs were able to mediate the expansion of ‘CD4’CD25’FoxP3’ Tregs. Indeed, this finding was consistent with the significant correlation between the frequency of MDSCs and Tregs in HAART-naive HIV progressors. On the other hand, MDSCs derived from HIV progressors dramatically decreased the proliferative capacity of cytotoxic (CD8’) T cells of both healthy and HIV-infected controllers. This was observed after co-culturing of MDSCs derived from HIV-infected progressors with phytohemagglutinin (PHA)-activated CD8’ T cells from healthy individuals and MDSCs of HIV-infected controllers with CD8’ T cells stimulated with Gag/Nef-peptide which significantly reduced their proliferative capacity when compared to incubation with MDSC-depleted PBMC from HIV-infected progressors, both of which can limit anti-HIV immune responses resulting in virus persistence and consequently disease progression. These data indicate that the direct and indirect immunosuppressive activities of MDSCs are inseparable events, which, in part, reflects the complexity of the immune response network.

To study the suppressive mechanisms of MDSCs derived from HIV-infected patients, Vollbrecht et al. [29] have shown that PMN-MDSCs of their cohorts express IL-4 receptor alpha (IL-4Rα), which paradoxically was shown to be expressed in immunosuppressive M-MDSCs derived from cancer patients with suppressive functions [41]. Initially, this information provided an indication that, during HIV infection, PMN-MDSCs could have suppressive effects on T cells, at least in part through the IL-4Ra pathway. However, it is important to remember that the primary objective of the study of Vollbrecht et al. was to determine whether MDSCs are expanded during chronic HIV infection or not, and, if so, to determine whether such expansion may have a role in HIV disease progression. This explains why this study did not focus on the suppressor mechanisms by which MDSCs could inhibit anti-HIV immune responses.

A year later, Qin et al. [30] were the second group to study the impact of MDSC expansion during chronic HIV infection, in a more comprehensive manner. Regarding the mechanism(s) by which M-MDSCs mediate their suppressive effects, Qin et al. [30] reported that there was a moderate but significant association between M-MDSC expansion and detection of CD38’CD8’ T cell subsets, which is known to be associated with disease progression markers (i.e. high viral load, loss of CD4’ T cells and abnormal chronic immune activation). In HIV infection, the expansion of CD8’ T cells expressing activation markers such as CD38 was shown to be associated with disease progression in primary and chronic HIV-1 infections [42,43]. This suggests that MDSCs could mediate their suppressive activity indirectly, at least in part, via stimulating such an activated/exhausted subset of T cells.

Unlike M-MDSCs from healthy individuals, Qin et al. [30] showed that M-MDSCs from HIV patients exhibit suppressive effects on cell proliferation and IFN-γ production for both helper (CD4) and cytotoxic (CD8) T cells in a dose- and contact-dependent manner. Importantly, this supports the idea that MDSCs function differently in pathological

---

**Figure 1.** Expansion of MDSCs and the pathogenesis of HIV infection. Upon HIV infection, MDSC expansion is driven by different factors including HIV particles (infectious or non-infectious), HIV proteins (e.g. HIV gp120, Nef and Tat proteins), host factors (e.g. inflammatory cytokines and molecules) and microbial byproducts (e.g. lipopolysaccharide ‘LPS’) upon microbial translocation. These pathologically expanded MDSCs can suppress both the innate (i.e. antigen-presenting cells ‘APC’ such as dendritic cells ‘DC’, macrophages ‘MΦ’, polymorphonuclear neutrophils ‘PMN’ and natural killer ‘NK’ cells) and adaptive immune responses (both the helper and cytotoxic T cells). As a result, immune responses against HIV-infected cells will be restricted, which, in turn, will enhance HIV replication, one way or another, thus entering a vicious cycle leading to disease progression.
arginase in M-MDSCs was associated with increased levels compared with healthy subjects. This increase in the activity of arginase was observed in PBMC from HIV patients compared with healthy subjects. This increase in the activity of arginase in M-MDSCs was associated with increased levels of Arg1 expression (the gene that encodes for arginase; which is an enzyme responsible for arginase 1 'ARG1' activity). By contrast, when comparing the levels of NO in the plasma of HIV patients and healthy subjects, there was a decrease in NO levels in the plasma from HIV patients. This decrease in NO levels was coupled with a decrease in the level of iNos expression (the gene that encodes for iNOS enzyme; which is an enzyme responsible for the production of NO). These results indicate that HIV infection could induce the expression of Arg1 while repressing the expression of iNos in M-MDSCs. Lastly, there was no obvious difference in ROS levels between HIV patients and healthy subjects. This indicates that the suppressive effects were due to the induction of Arg1. The study of Qin et al. [30] also showed that in vitro HIV infection of normal PBMC obtained from healthy individuals led to a remarkable increase in M-MDSCs, indicating that HIV infection contributes directly to the expansion of MDSCs. Furthermore, the administration of recombinant Tat protein to PBMC cultures from healthy subjects resulted in a remarkable increase in MDSC generation, suggesting that Tat protein by itself could play a role in MDSC expansion during HIV infection. This report was the first of its kind to demonstrate that viral proteins, namely HIV Tat protein, can mediate MDSC expansion separately from the viral replication. Perhaps, if they measured the levels of Tat protein and compared them to the frequency of MDSCs in peripheral blood of HIV patients, a stronger correlation can be made, hence we suggest future investigations to clearly determine the impact of Tat protein on the expansion of MDSCs.

Qin et al. [30] also reported that M-MDSCs express high levels of HIV co-receptors, namely CCR5 and CXCR4, while expressing lower levels of CD4, and that M-MDSCs have the potential to be directly infected by the virus. Although this possibility exists, the virus seems to have no cytotoxic effects on MDSCs, especially because there is a positive association between MDSC counts and viral load. An additional interesting finding in this study was that MDSCs can also enhance viral replication in CD4+ T cells, since there was a significant increase in HIV-1 p24 antigen in supernatants of MDSCs/T-cell co-cultures with high MDSCs/T-cells ratios (1:1) compared to the low MDSCs/T-cell ratios (1:10). This enhancement was shown to be dependent on direct cell-to-cell contact. Taken together these data show that MDSCs not only participate in limiting specific T-cell anti-viral immune responses and mediating immune exhaustion, but also, they enhance viral replication, all of which can lead to viral persistence and disease progression, suggesting that targeting MDSCs could have a potential clinical implication.

To further understand how HIV dampens anti-HIV immune responses mediated by T cells that, in turn, lead to disease progression, Bowers et al. [31] have conducted their investigations on the most abundant leucocyte in the human body, namely the PMN. Although they reported no difference in the phenotype of neutrophils in healthy and HIV-infected patients, there was a significant increase in programmed death ligand-1 (PD-L1) expression on neutrophils of HIV patients, and as such, these PD-L1high neutrophils were described as immunosuppressor cells. In addition, they were isolated from the low-density (LD) gradient (i.e. monocytic fraction) which is consistent with the findings of Cloke et al. [45,46]. Furthermore, recent advances in MDSC characterization have revealed that MDSCs comprise a mixture of mature and immature myeloid cells (IMCs) with immunosuppressive function [7], and PMN-MDSCs are also isolated from the LD gradient. Although the exact aetiology of LD neutrophils remains unclear, some investigators believe that neutrophils could acquire this phenotype after degranulation, so that their density becomes similar to that of PBMC and thus may become co-segregated in the LD gradient of the mononuclear cell fraction. Accordingly, the neutrophils in the study by Bowers et al. can be described as PMN-MDSC or; at least, as PMN-MDSC-like cells. Bowers et al. [31] observed a significant association between PD-L1 expression and the viral load. This is, especially, true because the drop in viral load upon initiation of ART resulted in a significant decrease in the expression of PD-L1 on LD neutrophils. On the other hand, no differences were observed in PD-L1 expression on LD neutrophils between elite HIV-infected controllers (who naturally maintain HIV replication below the limit of detection (50 HIV RNA copies/ml by standard assays) and healthy subjects. This suggests that restoring normal MDSCs could play a role in controlling HIV infection, one way or another.

It goes without saying that the immunoregulatory function of PD-1/PD-L1-axis has become an attractive research area in recent years. In the study of Bowers et al. [31], the depletion of PD-L1high LD neutrophils (PMN-MDSC) from PBMC of HIV donors resulted in a significant increase in CD4+ and CD8+ IFN-γ-producing T cells. A comparable increase in IFN-γ production by T cells was also reported upon specific stimulation of PMN-MDSC-depleted PBMC samples, from HIV patients, with viral antigens (HIV-1 gag polypeptide pool), non-specific stimulation with PHA or anti-CD3/CD28 antibodies. This suggests that the inhibitory function mediated by this immunosuppressive population of neutrophils was independent of specific antigen stimulation. In addition, Bowers et al. [31] have shown that the elevation of PD-L1 expression on LD neutrophils is directly associated with T-cell exhaustion and immune-senescence markers, PD-1 expression on both CD4+ and CD8+ T cells and CD57 expression on CD4+ T cells. Furthermore, the expression level of PD-L1 on LD neutrophils directly correlates with the level of ARG-1 in plasma of HIV patients and indirectly with the expression of CD3ζ chain on T cells. In fact, ARG-1 is known to limit the responsiveness of T cells through downregulating the expression of CD3ζ chain by the depletion of a critical metabolite required for T-cell functions, namely L-arginine [47]. Of note, during antigen stimulation, the interaction of PD-1 expressed on T cells with PD-L1 expressed on different antigen-presenting cells, such as DCs and monocytes/macrophages, is known to suppress T-cell activation mediated by T-cell receptor (TCR).

Exposing DC, monocytes and other immune cells to activated/inactivated HIV particles and activation of
T-cell count and the frequency of MDSCs in HIV patients was reported by different groups; however, Tumino et al. [32] did not observe such correlations in PMN-MDSC frequency between HIV patients (different groups) with CD4+ T-cell count greater than 400 cells ml$^{-1}$. Still, HIV patients with CD4+ T-cell counts below 400 cells ml$^{-1}$ were shown to have a significant difference in PMN-MDSC frequency when compared to other HIV groups with CD4+ T-cell counts greater than 400 cells ml$^{-1}$. Importantly, Tumino et al. [32] delineated the direct role of PMN-MDSCs in downregulating the expression of CD3ζ chain in different T-cell populations (CD4+, CD8+, Vγ9 Vδ2T cells). This observation was consistent with the previous observation that HIV infection is associated with a remarkable reduction in CD3ζ chain expression on Vγ9 Vδ2T cells [58]. Interestingly, such roles played by PMN-MDSCs are not only restricted to HIV patients but also observed in cells isolated from healthy donors, suggesting that the effect on the expression of CD3ζ chain is a general feature of PMN-MDSCs. Furthermore, such effects were dependent on direct cell-to-cell contact, as demonstrated in in vitro studies. The study of Tumino et al. [32] also confirmed that downregulating the expression of CD3ζ chain on T-cells results in their hypo-responsiveness, i.e. reduced IFN-γ production by T cells upon stimulation with specific (HIV-peptides; Gag and Nef) or non-specific (phosphoantigen) antigens. It is important to remember that downregulating the expression of CD3ζ chain on T cells is not an irreversible event. As such, depleting the PMN-MDSCs from T-cell cultures resulted in the restoration of CD3ζ chain expression on T cells and restoration of T-cell function (IFN-γ production). PMN-MDSCs were able to downregulate the expression of CD3ζ chain by interfering with E74-like ETS transcription factor 1 (ELF-1), a transcription factor involved in regulating the expression of CD3ζ molecule [65,66]. Yet, the exact mechanism(s) by which PMN-MDSCs downregulate the expression of CD3ζ chain remains to be determined. However, the amino acid, L-arginine, seems to play a role in this context, especially, because L-arginine starvation is reported to decrease the expression of CD3ζ molecule on Jurkat T cells and such reduction was associated with their limited response to antigen stimulation [67]. Since PMN-MDSCs express high levels of ARG-1, which, in turn, leads to increased activity of arginase and thus L-arginine catabolism and depletion from the microenvironment, we postulate that PMN-MDSCs could mediate the downregulation of CD3ζ chain expression, at least in part, through the expression of ARG-1. Therefore, targeting such immunoregulatory cell populations could be of potential therapeutic implication for controlling HIV infection.

With respect to the already established function of MDSCs in that they inhibit T-cell functions, Garg et al. [34] have also shown that coculturing of HIV gp120-expanded CD33+ cells with autologous CD4+ and CD8+ T cells can significantly limit their capacity to produce IFN-γ, when compared to controls (CD33+ cells alone). Importantly, such inhibitory function was dependent on direct cell-to-cell contact. As previously mentioned, MDSCs could mediate their suppressive function using the biochemical and metabolic soluble mediators such as ROS, iNOS and ARG-1 [68–70]. In the study of Garg et al. [34], the mechanism(s) by which gp120-expanded MDSCs mediated their inhibitory function (i.e. inhibition of IFN-γ production by T cells) was dependent only on iNOS and ROS, since the neutralization of these two, but not ARG-1, upon coculturing of gp120-expanded MDSCs
with CD4+ or CD8+ T cells restored their capacity to produce IFN-γ. Another important soluble molecule that has the capacity to suppress immune responses including those mediated T cells is IL-10 (please refer to our recent review for more details about the immunosuppressive role of MDSCs/IL-10 [6]). IL-10 is produced by a wide range of immune cells including CD4+ T cells, particularly Treg cells, and MDSCs [6]. The production of IL-10 is elevated during HIV infection, and such elevation was shown to be directly associated with virus replication [71]. To delineate whether gp120-expanded MDSCs contribute to this elevation in IL-10 production, Garg et al. [34] showed that neither gp120-expanded MDSCs nor CD4+ T cells were able to produce IL-10 when cultured alone. Interestingly, coculturing the gp120-expanded MDSCs with CD4+ T cells resulted in the release of copious amounts of IL-10, and according to the intracellular staining used to detect IL-10 production, CD4+ T cells but not the gp120-expanded MDSCs were identified to be the source of IL-10 production. The last finding in this study was that gp120-expanded MDSCs can mediate the expansion of Treg cells, the primary source of IL-10 in this study. These findings indicate that expanded MDSCs contribute to immune suppression during HIV infection, at least in part, through mediating the expansion of Treg cells. Undoubtedly, using purified and isolated cells does not represent the complexity of the interaction in different cell populations involved in MDSC mediation in the blood of HIV patients, and thus, the experimental system used in this study is considered a limitation. As such, Garg et al. [34] suggested to use whole blood PBMC to overcome this limitation in future investigations.

3.2. Myeloid-derived suppressor cells during acute human immunodeficiency virus infection

Tumino et al. [37] were among the first groups to study the role of MDSCs during acute HIV infection. They did not find any correlation between the frequency of PMN-MDSCs and immune activation (T-cell activation) or inflammatory factors, thereby, ruling out the possibility of immune activation being the driving force that regulates the expansion of MDSCs during the early phase of HIV infection. In contrast, this possibility still exists when discussing MDSC expansion during the chronic phase of HIV infection. In particular, this is because Tumino et al. [37] observed a correlation between immune activation markers such as soluble IL-2 receptor (sIL-2R; which is a marker of immune activation and disease progression in HIV-infected individuals [72,73]), interferon alpha (IFN-α) and monocyte chemoattractant protein-1 (MCP-1) among others, and PMN-MDSC frequency in chronic-infected HIV patients. To investigate the soluble factors that could regulate MDSC expansion, a panel of 40 cytokines and growth factors were examined in both acutely and chronically infected patients [37]. Interestingly, only tumour-necrosis factor-related apoptosis-inducing ligand (TRAIL), which is a multifunctional member of the tumour-necrosis factor cytokine-superfamily, closely related to Fas ligand, and is known to induce apoptosis in several cell types including MDSCs [74–76]) was shown to be correlated with the frequency of PMN-MDSCs in acutely infected HIV patients, especially the Fiebig stages II/III and IV. Although the levels of plasma TRAIL were higher in both groups when compared to those of healthy subjects, there was no difference between acutely and chronically infected HIV patients. Unexpectedly, in contrast with chronic HIV infection, a negative correlation between TRAIL levels and PMN-MDSC frequency was observed in acute phases of HIV infection, suggesting that TRAIL could play a different role in the context of MDSC expansion according to the disease stage. In order to clarify this unexpected observation, they investigated the role of GM-CSF in this context for two reasons. First, according to their results, GM-CSF was the only cytokine it’s the level of which was significantly higher in chronically infected HIV patients when compared to acutely infected patients. Second, this cytokine plays a critical role in mediating the expansion of MDSC [62]. As expected, culturing of PBMC from acutely infected patients with GM-CSF and recombinant-TRAIL (r-TRAIL) abrogated TRAIL-mediated apoptosis, explaining the positive correlation between the frequency of PMN-MDSCs and the plasma level of TRAIL during chronic HIV infection. Although Tumino et al. [37] observed no correlation between the frequency of PMN-MDSCs and viral load or CD4+ T-cell count in both acutely and chronically infected HIV patients, the negative impact of PMN-MDSCs on HIV disease progression cannot be excluded. This is mainly because the CD4+ T-cell counts of the enrolled patients (in all groups) in their study was relatively high. However, they provided evidence that the expansion of PMN-MDSCs starts very early during HIV infection, and this expansion continues to the chronic stage of HIV infection. Furthermore, PMN-MDSC expansion during HIV infection is influenced by the clinical stage and the host immune responses including TRAIL and GM-CSF.

Zhang et al. [33] also confirmed that MDSCs, PMN-MDSCs in particular, are expanded during the early and late infection stages of HIV. In agreement with previous studies, they have shown that a significant association exists between the level of PMN-MDSCs and disease progression markers. For example, the PMN-MDSC level negatively correlates with CD4+ T-cell counts, and positively correlates with viral load and immune activation manifested by inducing CD38+CD8+ T-cell populations. It must be remembered that the fact that CD38+CD8+ T cells play a critical role in the pathogenesis of HIV infection has been well established and could also be used as a marker of disease progression in: primary HIV infection; T-cell activation; residual virus replication in chronically HIV-infected patients receiving ART; virological failure in HIV-infected youths and children receiving ART; and HIV dissemination into the central nervous system [42,77–81]. However, a higher level of PMN-MDSCs was observed in HIV patients with lower CD4+ T-cell counts during the acute phase of infection when compared to patients with high CD4+ T-cell counts, reflecting the importance of CD4+ T cells in shaping the clinical status. Additionally, in agreement with previous studies, Zhang et al. [33] also confirmed that PMN-MDSCs derived from HIV patients can suppress the proliferation and IFN-γ production of TCR-stimulated CD8+ T cells. To determine the mechanism by which PMN-MDSCs could mediate immune suppression during HIV infection, Zhang et al. questioned whether PD-L1 and galectin-9 (Gal-9), which are co-inhibitory molecules that play a notable role in immune-related disorders [82], are expressed on MDSCs or not. Consequently, they confirmed a significant increase in the expression of PD-L1 but not Gal-9 on PMN-MDSCs which could be mediated in part through IL-10. Furthermore, they demonstrated the direct association between PD-L1 expression on PMN-MDSCs and the expression
of its ligand on CD8+ T cells, namely PD-1, during the primary and chronic phases of HIV infection. This indicates that the PD-1/PD-L1 axis is involved in the suppressive function of MDSCs, especially since blocking this axis using a PD-L1 blocking antibody resulted in a notable restoration of CD8+ T-cell responses against HIV and thus controlling HIV disease progression.[29,35] (figure 3). Therefore, targeting MDSCs could result in restoring T responses against HIV and thus controlling HIV disease progression (figure 4).

3.3. Myeloid-derived suppressor cells expansion during simian immunodeficiency virus infection

To address the kinetics of MDSCs during SIV infection in rhesus macaques, a non-human primate model of HIV...
Figure 3. MDSCs inhibit anti-HIV immune responses mediated by T cells. MDSCs could inhibit T cell responses against HIV-infected cells via direct cell-to-cell engagement. Alternatively, MDSCs could inhibit T cells indirectly via secreting anti-inflammatory molecules such as interleukin-10 (IL-10) and transforming-growth factor beta (TGF-β), or via mediating the expansion of other immunoregulatory cells such as regulatory T (Treg) cells. As the case with MDSCs, Treg cells could engage with T cells directly or secrete immunoregulatory molecules to suppress T cell responses against HIV-infected cells. Indeed, MDSCs could directly or indirectly engage with T cells and suppress anti-HIV immune responses mediated by T cells via one or more of the following mechanisms: (1) mediating the expansion of pathologically activated CD8+CD38+ T cells and or Treg cells; (2) activating arginase-1 (ARG1), which is known to decrease the expression of CD3ζ chain on T cells that, in turn, limits the activation of T cells; (3) enhancing the expression of immunoregulatory checkpoint proteins, namely programmed death cell protein 1 (PD-1) and its ligand (PD-L1); (4) activating interleukin-4 receptor alpha (IL-4Rα) pathway; (5) production of immunosuppressor molecules such as IL-10 and tumour-growth factor β (TGF-β).

Figure 4. MDSC expansion in health and HIV infection. Under normal physiological conditions, in the absence of inflammation, MDSCs remain at low levels as seen in case number 1. In other normal physiological conditions such as pregnancy and lactation [7], the levels of MDSCs are increased to protect the fetus from its mothers' immune system. After delivery, the levels of MDSCs return to the level before pregnancy as seen in case number 2. In the pathological settings such as HIV infection, as seen in case number 3, there is a direct association between MDSC expansion and HIV disease progression. Therefore, restoring normal MDSC levels, therapeutically, could result in control of HIV disease progression, as seen in the proposed case number 4.
infection was recently used by Dross et al. [40]. One major finding of this study was that MDSCs are expanded during the early phase of SIV infection and such expansion continues to the chronic phase of infection. The levels of MDSCs, particularly PMN-MDSCs, were shown to be significantly increased post-SIV infection when compared to those measured before SIV infection. Importantly, such expansion was shown to be directly associated with viral load set-point, a critical marker of disease progression [84]. However, they observed no significant correlation between MDSC expansion and viral load or CD4+ T-cell counts. This contradicts the results of human studies in that the viral load in ART-naive chronically infected HIV patients correlates with MDSC frequencies [29–31]. In part, this may be due to the fact that SIV-infected rhesus macaques used in the study were mostly aviremic, unlike ART-naive chronically infected HIV patients which were viremic, since rhesus macaques were treated with ART as early as six weeks post-SIV infection. This indicates that prolonged exposure to viremia in ART-naive chronically infected HIV patients may act as a critical factor that influences the elevation of inflammatory cytokines and thus the induction of MDSC generation and accumulation. On the other hand, the absence of correlation between CD4+ T-cell counts and MDSC frequency in the study could be due to the elevation in CD4+ T-cell counts in SIV-infected animals (average of 1150 CD4 per ml) versus that in human studies (average of greater than 500 CD4 per ml) [29–31,40]. This is especially true since a significant correlation between MDSC frequency and CD4+ T-cell counts may wane in healthy individuals and HIV-infected humans or SIV-infected animals with high CD4+ T-cell counts [29–31,40]. To determine the impact of ART on MDSCs, Dross et al. have shown that the levels of MDSCs remained significantly high after 31 weeks of ART initiation. Cessation of ART resulted in a remarkable increase in MDSCs and such increase remained after 30 weeks post-ART cessation. Yet, the major purpose of this study was to investigate the connection between MDSC expansion and reduced T-cell proliferation capacity during SIV infection, especially since the proliferative capacity of T cells is considered to be the strongest independent predictor factor of disease progression in HIV patients [85]. Unsurprisingly, similar to what has already been established in human investigations, MDSCs obtained from SIV-infected rhesus macaques were able to suppress T-cell functions and reduce their proliferative capacity (as measured by the expression of CD3 and Ki67) at different time points (3 weeks pre-SIV infection, 3 weeks post-SIV infection, 31 weeks post-ART treatment and 19 weeks post-ART interruption) [40]. With respect to the distribution of MDSCs in peripheral lymphatic tissues or the so-called secondary lymphoid organs (lymph nodes and spleen), which are the sites where T cells become activated, there was no increase in MDSC frequency in the lymph nodes but not the spleen, when compared to the peripheral blood. Additionally, MDSCs from the spleen of SIV-infected rhesus macaques were shown to be as suppressive as the MDSCs of peripheral blood. It is worth mentioning that the splenic infiltrated MDSCs of tumour-bearing mice are less suppressive than those obtained from the tumour site [86]. This seems to be a remarkable difference between retroviral infection and cancer. In the context of determining the force that drives the expansion of MDSCs during the course of SIV infection, Dross et al. [40] have shown that unlike viral load, inflammatory cytokines (such as TNFα, IL-1β, IL-6 and MIP-1α/β) were the major drivers of MDSC expansion over the viral particles. Generally speaking, it has been shown that the frequency of MDSCs increases as the disease progresses in SIV-infected rhesus macaques, suggesting that MDSCs play a critical role in the pathogenesis of SIV infection [40].

4. Myeloid-derived suppressor cells as a therapeutic target in human immunodeficiency virus infection

It is clearly evident that the expansion of MDSCs during the course of HIV infection has detrimental impacts on HIV persistence and disease progression, at least in part, through hampering anti-HIV immune responses mediated by T cells [29–35,83,87]. Also, MDSCs per se could stand as a barrier to reconstitute immune responses in successfully antiretroviral treated HIV patients [35]. Accordingly, targeting MDSCs could provide a promising avenue to enhance and reconstitute anti-HIV immune responses, both of which can participate in controlling HIV infection (figure 4). This is true, especially, if we took into consideration that the expansion of MDSCs accompanies HIV infection from the early days after infection to the late AIDS phase [30,33,37–39]. In general, targeting MDSCs could be achieved by: first, targeting MDSCs for elimination; second, targeting the suppressive function of MDSCs; and/or third, targeting their recruitment to the site of inflammation. The first one could be achieved by targeting factors that regulate their expansion which include viral (gpp120, Tat and Nef proteins), host (e.g. inflammatory cytokines, regulatory molecules and transcription factors among others) and microbial (e.g. LPS) factors [30,34,35,83,88–90]. The second one could be achieved for example, by targeting immune checkpoint proteins (PD-1/ PD-L1), immunoregulatory cytokines and/or other molecules. The third therapeutic approach could harness, for example, certain chemokine inhibitors to prevent the recruitment of MDSCs to the site of active HIV replication such as the lymphatic tissues. Unfortunately, there are no clinical trials that assess any of the previously mentioned strategies in the context of HIV infection. However, in cancer settings, different classes of drugs that target MDSCs have been used in clinical trials. With respect to anti-cancer candidate drugs that target MDSCs for elimination, for example, all-trans retinoic acid, certain tyrosine kinase inhibitors and TRAIL-R2 agonists were successfully used to eliminate MDSCs in cancer patients [91–96]. With respect to targeting the suppressive function of MDSCs, using certain phosphodiesterase inhibitors [97,98] and STAT3 inhibitors [99] has been reported to reduce the suppressive activity of MDSCs in cancer patients. Finally, different classes of drugs belong to CCR5 antagonists [100], S100 protein antagonists [101], CCL2 inhibitors [22] and VEGF inhibitors [102] were shown to block the recruitment of MDSCs to the site of inflammation as a strategy to limit the inhibitory effect of MDSCs in cancer tissues. The promising results obtained from targeting MDSCs in cancer settings at the clinical level suggest that such therapeutic approaches/drugs could be used in the context of HIV infection in the future.
5. Conclusion

Taken together, there is no doubt that MDSCs are expanded during the acute and chronic phases of HIV and SIV infections in humans and rhesus macaques, respectively. Such expansion is regulated by different factors, including host, viral and microbial factors (figures 1 and 2). Importantly, the expansion of MDSCs during HIV infection is associated with disease progression. This work aimed to address the mechanisms by which MDSC expansion contributes to the pathogenesis of HIV infection. As such, we included all the published studies related to the pathological role played by MDSCs during HIV infection to the date of paper submission. Regarding the mechanisms by which MDSCs sabotage anti-HIV immune responses in these studies, great variation existed in the results, although they were consistent with the findings observed in other pathological conditions. In other words, under certain circumstances, MDSCs induce their immunosuppressive activity directly upon cell-to-cell engagement through PD-1/PD-L1-axis, or indirectly by secreting immunosuppressant molecules such as IL-10, activating or mediating the expansion of Treg cells and exhausted CD8⁺CD38⁺ T cells, or even through a combined event (figure 3). Activation of IL-4Rα pathway and ARG1 were also reported. Indeed, the activation of ARG1 can reduce the expression of CD3ζ chain, which is a part of the TCR, on T cells, thereby, reducing the activation of T cells upon antigen stimulation. However, the research field on MDSCs during HIV infection is still in its infancy because of the following reasons: (i) the expansion of MDSCs is still underdetermined in anatomical compartments other than peripheral blood [103]; (ii) the suppressive activity of MDSCs has been investigated only in T cells but not in other immune cells such as DCs, monocytes/macrophages and NK cells; (iii) there are no investigations about the suppressive activities of MDSCs in HIV-infected elite controllers (a group of patients that control HIV replication to a level below the limit of detection by standard assays); and (iv) targeting MDSCs therapeutically has neither been investigated in pre-clinical nor in clinical sides during HIV infection. Therefore, future investigations should address these issues to fill the gap of knowledge in this important area of research.

Data accessibility. This article has no additional data.

Authors’ contributions. M.M.Y. contributed in writing all sections and in editing the final version of this manuscript. N.M.A. and H.D. contributed in writing the introduction and in editing the final version of this manuscript.

Competing interests. We declare we have no competing interests.

Funding. We received no funding for this study.

References

1. Yaseen MM, Abuharfeil NM, Yaseen MM, Shabsoug BM. 2018 The role of polymorphonuclear neutrophils during HIV-1 infection. Arch. Viral. 163, 1–21. (doi:10.1007/s00705-017-3569-9)
2. Alqudah MAY, Yaseen MIM, Yaseen MMS. 2016 HIV-1 strategies to overcome the immune system by evading and invading innate immune system. HIV/AIDS Rev. 15, 1–12. (doi:10.f1/rev.hivar.2015.07.004)
3. Hillson S, Arleevskaya MI, Blanco P, Bordron A, Brooks WH, Cebrón JV, Kawi S, Vivier E, Renaudineau Y. 2020 The innate part of the adaptive immune system. Clin. Rev. Allergy Immunol. 58, 151–154. (doi:10.1007/s12016-019-08740-1)
4. Gourbal B, Pinaud S, Beckers GJMJ, Van Der Meer JWJ, Grenath U, Netea MG. 2018 Innate immune memory: an evolutionary perspective. Immunol. Rev. 283, 21–40. (doi:10.1111/imr.12647)
5. Huang H, Lu Y, Zhou T, Gu G, Xia Q. 2018 Intrahepatic MDM2 in hepatitis C: implications for therapy. Front. Immunol. 9, 2401. (doi:10.3389/fimmu.2018.02401)
6. Yaseen MM, Abuharfeil NM, Homa D, Daoud A. 2020 Mechanisms of immune suppression by myeloid-derived suppressor cell: the role of IL-10 as a key immunoregulatory cytokine. Open Biol. 10, 200111. (doi:10.1098/rsob.200111)
7. Yaseen MM, Abuharfeil NM, Darmani H, Daoud A. 2020 Recent advances in myeloid-derived suppressor cell biology. Front. Med. 15, 232–251. (doi:10.3389/fmed.2020.0122)
8. Jeffries AM, Marshall L. 2020 Cytosolic DNA sensors and CNS responses to viral pathogens. Front. Cell Infect. Microbiol. 10, 578. (doi:10.3389/fcimb.2020.578)
9. Wu J, Chen ZJ. 2014 Innate immune sensing and signaling of cytosolic nucleic acids. Annu. Rev. Immunol. 32, 461–488. (doi:10.1146/annurev-immunol-032713-120156)
10. Rathinam V A, Vanaja SK, Fitzgerald KA. 2012 Regulation of inflammasome signaling. Nat. Immunol. 13, 333–342. (doi:10.1038/nl.2237)
11. Kawai T, Akira S. 2010 The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat. Immunol. 11, 373–384. (doi:10.1038/nri.1863)
12. Takeuchi O, Akira S. 2010 Pattern recognition receptors and inflammation. Cell 140, 805–820. (doi:10.1016/j.cell.2010.01.022)
13. Suresh R, Mosser DM. 2013 Pattern recognition receptors in innate immunity, host defense, and immunopathology. Adv. Physiol. Educ. 37, 284–291. (doi:10.1152/advan.00058.2013)
14. Sereznii CH, Ballinger MN, Aronoff DM, Peters-Golden M. 2008 Cyclic AMP: master regulator of innate immune cell function. Am. J. Respir. Cell Mol. Biol. 39, 127–132. (doi:10.1165/rcmb.2008-0911TR)
15. Barton JL, Berg T, Didon L, Nord M. 2007 The pattern recognition receptor Nod1 activates CCAAT enhancer binding protein beta signalling in lung epithelial cells. Eur. Respir. J. 30, 214–222. (doi:10.1183/09031936.0043906)
16. Paiva CN, Bozza MT. 2014 Are reactive oxygen species always detrimental to pathogens? Antioxid. Redox Signal. 20, 1000–1037. (doi:10.1089/ars.2013.5447)
17. Pati S, Chowdhury A, Mukherjee S, Guin A, Mukherjee S, Sa G. 2020 Regulatory lymphocytes: the dice that resolve the tumor endgame. Appl. Cancer Res. 40, 1–9. (doi:10.1186/s41241-020-00091-0)
18. Gutierrez C et al. 2019 Analysis of the dysregulation between regulatory B and T cells (Breg and Treg) in human immunodeficiency virus (HIV)-infected patients. PLoS ONE 14, e0213744. (doi:10.1371/journal.pone.0213744)
19. Cronkite DA, Strutt TM. 2018 The regulation of inflammation by innate and adaptive lymphocytes. J. Immunol. Res. 2018, 1467538. (doi:10.1155/2018/1467538)
20. Schett G, Neurath MF. 2018 Resolution of chronic inflammatory disease: universal and tissue-specific concepts. Nat. Commun. 9, 3261. (doi:10.1038/s41467-018-05800-6)
21. Pardiini M, Muller-Trutwin M. 2013 HIV-associated chronic immune activation. Immunol. Rev. 254, 78–101. (doi:10.1111/imr.12079)
22. Rajasirai R, Khoury G, Kamalzadah A, French MA, Cameron PU, Lewin SR. 2013 Persistent immune activation in chronic HIV infection: do any interventions work? AIDS 27, 1199–1208. (doi:10.1097/QAD.0b013e32835ecb8b)
23. Sokoya T, Steel HC, Nieuwoudt M, Rossouw TM. 2017 HIV as a cause of immune activation and immunosenescence. Mediators Inflamm. 2017, 6825493. (doi:10.1155/2017/6825493)
24. Weiss L et al. 2010 Relationship between regulatory T cells and immune activation in human immunodeficiency virus-infected patients.
32. Tumino N et al. 2019 Role of regulatory T cells in the pathogenesis of HIV-1 infection. Retrovirology 6, 1371/journal.pone.0011659.
33. Zhao J, Ren JP, Pion M. 2016 Functional mechanisms of Treg in the context of HIV infection and the innate phase of immune suppression. Front. Immunol. 7, 192. (doi:10.3389/fimmu.2016.00192)
34. Cao W, Jamieson BD, Hultin LE, Hultin PM, Detels R. 2009 Chronic progressive HIV-1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. J. Infect. Dis. 198, 757–766. (doi:10.4049/jimmunol.1600759)
35. Agrati C et al. 2019 Myeloid derived suppressor cells expansion persists after early ART and may affect CD4 T cell recovery. Front. Immunol. 10, 1886. (doi:10.3389/fimmu.2019.01886)
36. Heffron H, Hel Z. 2013 Expansion of monocytic myeloid-derived suppressor cells increased in early phases of primary HIV infection depending on TRAIL plasma level. AIDS 27, 1521–1531. (doi:10.1097/QAD.0b013e32835d62a2)
37. Tumino N et al. 2017 Granulocytic myeloid-derived suppressor cells increased in early phases of primary HIV infection depending on TRAIL plasma level.
63. Hwu P, Du MX, Lapointe R, Do M, Taylor MW, Young HA. 2000 Indoleamine 2,3-dioxygenase production by human dendritic cells results in the inhibition of T cell proliferation. J. Immunol. 164, 3596–3599. (doi:10.4049/jimmunol.164.7.3596)

64. Barron L et al. 2013 Role of arginine 1 from myeloid cells in th2-dominated lung inflammation. PLoS ONE 8, e61961. (doi:10.1371/journal.pone.0061961)

65. Juang YT, Solomou EE, Reilahan B, Tsokos GC. 2002 Phosphorylation and O-linked glycosylation of EIF-1 leads to its translocation to the nucleus and binding to the promoter of the TCR zeta-chain. J. Immunol. 168, 2865–2871. (doi:10.4049/jimmunol.168.6.2865)

66. Barron L, Juang YT, Tenbrock K, Nambiar MP, Gourley MF, Du MX, Lapointe R, Do M, Taylor MW, Hwu P, Schulte C, Meurer M. 1989 Soluble IL-2 receptor CD4+ T cell activation during HIV infection. J. Immunol. 142, 2639. (doi:10.4049/jimmunol.142.6.2639)

67. Rodriguez PC, Zea AH, Culotta KS, Sierra R, Ochoa AC. 2009 Arginase I-CD3ζ, the 123123 form of Elf-1 is responsible for the decreased expression of TCR zeta-chain in patients with systemic lupus erythematosus. J. Immunol. 165, 6048–6055. (doi:10.4049/jimmunol.165.10.6048)

68. Rodriguez PC, Zabaleta J, Sierra R, Ochoa AC. 2002 Defective production of functional 98-kDa form of Eif-1 is responsible for the decreased expression of TCR zeta-chain in patients with systemic lupus erythematosus. J. Immunol. 169, 6048–6055. (doi:10.4049/jimmunol.169.10.6048)

69. Tacke RS, Lee HC, Goh C, Courtney J, Polyak SJ, Schaefer U, Voloshanenko O, Willen D, Walczak H. 2015 Soluble E2F4 promotes myeloid-derived suppressor cell expansion in oncology. Crit. Rev. Oncol. Hematol. 97, 49–59. (doi:10.1016/j.critrevonc.2015.05.006)

70. Benito JM, López M, Lozano S, Martínez P, González-Lahoz J, Soriano V. 2004 CD38 expression on CD8+ lymphocytes as a marker of residual virus replication in chronically HIV-infected patients receiving antiretroviral therapy. AIDS Res. Hum. Retroviruses 20, 227–239. (doi:10.1089/aid.2004.0299)

71. Schaefer U, Voloshanenko O, Willen D, Walczak H. 2007 TRAIL: a multifunctional cytokine. Front. Biosci. 12, 3813–3824. (doi:10.2741/2354)

72. Priceputu E, Cool M, Bouchard N, Caceres-Cortes JR, Lowell CA, Hamza Z, Jolicoeur P. 2021 HIV-1 Nef induces Hck/Lyn-dependent expansion of myeloid-derived suppressor cells associated with elevated interleukin-17/CXCL12 levels. J. Virol. 95, e0047121. (doi:10.1128/JVI.00471-21)

73. 2015 Long noncoding RNA RUNXOR promotes myeloid-derived suppressor cell expansion and functions via enhancing immunosuppressive molecule expressions during latent HIV infection. J. Immunol. 196, 2052–2060. (doi:10.4049/jimmunol.2001008)

74. Navedoza N, Fishman M, Sherman S, Wang X, Beg AA, Gabrilovich DI. 2007 Mechanism of all-trans retinoic acid effect on tumor-associated myeloid-derived suppressor cells. Cancer Res. 67, 11 021–11 028. (doi:10.1158/0008-5472.CAN-07-2993)

75. Kavirati S et al. 2020 Ibrutinib treatment inhibits breast cancer progression and metastasis by inducing conversion of myeloid-derived suppressor cells to dendritic cells. Br. J. Cancer 122, 1005–1013. (doi:10.1038/s41416-020-0743-8)

76. Heine A et al. 2016 The induction of human myeloid derived suppressor cells through hepatic stellate cells is dose-dependently inhibited by the tyrosine kinase inhibitors nilotinib, dasatinib and sorafenib, but not sunitinib. Cancer Immunol. Immunother. 65, 273–282. (doi:10.1007/s00262-015-1790-5)

77. Kao J, Ko EC, Eisenstein S, Sikora AG, Fu S, Chen S. 2011 Targeting immune suppressing myeloid-derived suppressor cells in oncology. Crit. Rev. Oncol. Hematol. 77, 12–19. (doi:10.1016/j.critrevonc.2010.02.004)

78. Weed DT et al. 2015 Tadalafil reduces myeloid-derived suppressor cells and regulatory T cells and promotes tumor immunity in patients with head and neck squamous cell carcinoma. Clin. Cancer Res. 21, 39–48. (doi:10.1158/1078-0432.CCR-14-1711)

79. Reiner MJ et al. 2018 STAT3 antisense oligonucleotide AZD9150 in a subset of patients with heavily pretreated lymphoma: results of a phase 1b trial. J. Immunother. Cancer 6, 119. (doi:10.1186/s40425-018-0436-5)

80. Nishikawa G, Kawada K, Nakagawa J, Toda K, Ogawa R, Inamoto S, Mizuno R, Itatani Y, Sakai Y. 2019 Bone marrow-derived mesenchymal stem cells promote colorectal cancer progression via...
