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Chapter

Macrophages and HIV/AIDS Pathogenesis: Lessons from the Rhesus Macaque Model

Elizabeth S. Didier and Marcelo J. Kuroda

Abstract

Destruction of $CD4^+$ T cells is a primary cause of immunodeficiency in Human Immunodeficiency Virus (HIV)-infected humans and Simian Immunodeficiency Virus (SIV)-infected rhesus macaques. Tissue macrophages, however, also contribute to AIDS pathogenesis. Studies on rhesus macaque lung revealed the presence of at least two types of macrophages comprising short-lived lung interstitial macrophages in the parenchyma that are not present in bronchoalveolar lavage (BAL), and the long-lived alveolar macrophages that predominate in BAL and rarely divide. Increased blood monocyte turnover was associated with death of infected short-lived tissue macrophages and terminal disease progression during AIDS. Antiretroviral therapy (ART) treatment of SIV-infected macaques effectively prevented active infection of short-lived macrophages in tissues and delayed disease progression. Interestingly however, longer-lived macrophages remained infected and survived despite ART. This suggests that the long-lived macrophages contribute to establishing a virus reservoir and that these infected persistent cells likely become dysregulated to promote chronic inflammation. Furthermore, macrophages are the predominant immunological cells in heart, adipose tissue, and lung, and these were primarily of the long-lived macrophage subset. Information about macrophages garnered from the SIV rhesus macaque model provides a basis to further develop intervention strategies that target macrophages for reducing chronic inflammatory co-morbidities and remove a contributing viral reservoir for achieving cure.

Keywords: Macrophage, HIV, SIV, pathogenesis, inflammation, rhesus macaque, virus reservoir

1. Introduction

Macrophages are immune cells located in tissues throughout the body that early in life, originate from the yolk sac during development and later from bone marrow-derived blood monocytes. Macrophages regulate inflammation and tissue repair to maintain or re-establish homeostasis in response to environmental exposures [1–4]. These cells exhibit tremendous plasticity and have been categorized in relation to their surface marker expression as well as pro- and anti-inflammatory responses

[5–7]. Results from murine studies initially drove the categorization of polarized macrophage populations and origins. These contributed to better understanding monocyte and macrophage differentiation and plasticity in humans [5, 6]. Nonhuman primates that physiologically resemble humans, also contributed to the in vivo characterization of short-lived and long-lived macrophages using approaches that are difficult to perform in humans [8]. In addition, studies using the SIV-rhesus macaque infection model that simulates the disease pathogenesis observed in humans with HIV infection have afforded further characterization of macrophages in vivo [9–11].

Prior to the era of antiretroviral therapy (ART) application, HIV or SIV infection commonly led to AIDS resulting from a loss of $CD4^+$ T cells [12, 13]. We also learned that an increase in monocyte turnover apparently required to replace damaged tissue macrophages, also correlated with terminal disease progression [14, 15]. The loss in $CD4^+$ T cells and infected short-lived macrophages facilitated the development of opportunistic infections and cancers leading to death. HIV- or SIV infected hosts administered ART, however, survive with low-to-undetectable plasma viral levels, but typically develop HIV/SIV-associated non-AIDS conditions resembling chronic inflammatory diseases that occur in the elderly but at an earlier age than in non-HIV/SIV-infected individuals, a process sometimes considered accelerated or accentuated aging [16]. Chronic inflammation is likely a result of macrophage dysregulation which can be more readily evaluated in rhesus macaques infected with SIV and treated with ART. And, although, $CD4^+$ T lymphocytes serve as a primary target of infection, HIV and SIV are lentiviruses that also infect macrophages, especially as $CD4^+$ T cells decline in numbers leaving macrophages more available for infection [3, 17–23]. These macrophage subpopulations appear to exhibit distinct functions during progressing stages of HIV/SIV infection [22, 24–26]. Thus, studies on SIV in rhesus macaques are relevant for addressing macrophage subpopulations and their roles in pathogenesis in vivo.

2. Macrophages plasticity

Metchnikoff described macrophages as large (macro) cells that eat (phage) particles and phagocytize dead cells, debris, and pathogens as a first-line of innate immune responses, which remains a primary function of these cells [5, 6]. Macrophages also present antigen in the context of major histocompatibility complex antigens to promote adaptive immune responses by lymphocytes. To facilitate these functions, macrophages exhibit plasticity or polarized activation states that impact secretion of and responsiveness to a wide range of cytokines and chemokines to regulate inflammation, tissue repair, and (re)establishment of homeostasis [5, 6]. The activation of macrophages to perform these functions is multi-dimensional and impacted by intrinsic and extrinsic tissue environmental stimuli. Exposures to extrinsic stimuli including cell debris, pathogenic agents, or toxins trigger innate immune responses, recruitment of immune cells and secretion of a wide array of chemokines and cytokines. These extrinsic stimuli were further characterized using in vitro models of macrophage polarization. At one end of this spectrum, Th1 signals such as interferon stimulate M1 "classical" macrophages to promote acute inflammatory responses in response to intracellular pathogens. On the other end of the spectrum, Th2 factors such as IL4 stimulate M2 "alternative" macrophages to exhibit anti-inflammatory and anthelmintic responses as well as wound healing or tissue repair. These categorizations were further refined into a range of intermediate activation states and chronic

or smoldering inflammation [6, 27]. Intrinsic factors impacting function consider macrophage origin via monocyte derivation versus resident embryonic progenitor status. Resident macrophages of embryonic yolk sac origin function in tissue remodeling and clearance of dead cells while monocyte-derived macrophages appear to function in microbial defense. It had long been believed that tissue macrophages are continually replaced by recruited blood monocytes that differentiate into tissue macrophages. More recently, studies in mice demonstrated that resident macrophages can undergo self-renewal [28]. In addition, monocyte-derived macrophages may acquire resident macrophage characteristics yet retain some epigenetic and transcriptional distinctions, suggesting that tissue environment may be more physiologically relevant than macrophage origin [6, 28, 29]. However, it is less clear and has been difficult to determine if embryonic-derived resident macrophages self-renew in nonhuman primates or humans throughout life [6, 28].

3. Tools to study macrophage populations in vivo in rhesus macaques

Rhesus macaque monocytes and macrophages express a wide range of biomarkers and cytokines / chemokines similar to those in humans, which can be identified via immune-detection and molecular biology methods. Surface biomarkers for CD14 and CD16 expression are commonly used to identify subpopulations of classical ($CD14^+$, $CD16^-$) pro-inflammatory, intermediate / transitional ($CD14^+$, $CD16^+$) and non-classical ($CD14^+/^-$, $CD16^-$) anti-inflammatory monocytes that traffic to tissues where they differentiate into macrophages [6]. Among surface markers, tissue macrophages express scavenger receptors (e.g. CD163), Toll-like receptors (TLR), scavenger and lectin receptors (e.g. CD163, CD206), glycoproteins (e.g. lysosomal-associated membrane protein CD68) and MHC class II moieties for recognition of pathogens and antigen presentation.

In addition to analyzing surface biomarker expression, these cells have been characterized as short-lived macrophages having recently differentiated from trafficking monocytes or as longer-lived (i.e. resident) macrophages. An approach to identify shorter-lived macrophages in rhesus macaques is to monitor the incorporation of thymidine analogues such as 5-bromo-2′-deoxyuridine (BrdU). BrdU has a short half-life of a few hours in vivo and incorporates in cells dividing during this time, including monocyte precursors in bone marrow. Immunostaining then can be applied to detect the recently dividing monocytes and follow their trafficking patterns from bone marrow to blood to tissues, as well as their turnover rates [14, 22, 24–26, 30, 31]. To detect longer-lived macrophages, dextran, a branched polymer of anhydroglucose can be administered. Phagocytic cells take up fluorescein-labeled dextran, and long-lived macrophages containing the conjugated dextran can be identified weeks or months later whereas the shorter-lived cells with dextran die in a few days and are replaced with recently-recruited unlabeled cells [22, 32].

4. SIV infection in nonhuman primates

SIV infections in nonhuman primates have served as invaluable animal models for HIV infection and AIDS research [12, 13, 33]. Nonhuman primates are similar to humans physiologically and immunologically. Advantages to using nonhuman primates in SIV/HIV research is the ability to closely regulate parameters such as time,

dose, and route of infection, as well as control for confounders such as smoking, diet, or illicit drug use. Experimental procedures for longitudinal tissue sampling, experimental vaccine testing, and therapeutic investigations also can be performed more readily in nonhuman primates. Naturally-infected nonhuman primate hosts such as African green monkeys and sooty mangabeys exhibit few clinical signs of disease from persistent or non-progressing SIV infection. Conversely, non-natural nonhuman primate hosts experimentally infected with SIV such as rhesus macaques, pigtail macaques, and cynomolgus macaques, exhibit a course of disease similar to that in humans with HIV infection. The differences between these non-pathogenic and pathogenic nonhuman primate models, respectively, provided opportunities to study comparative mechanisms of pathogenesis and immunity related to distinct outcomes of infection [34].

5. Increased monocyte turnover correlated to onset of terminal disease/AIDS in the absence of ART

Declining $CD4^+$ T cells is a key biomarker for immune-deficiency, morbidity, and mortality during HIV and SIV infections of rhesus macaques [13, 35]. However, in SIV-infected rhesus macaques, we observed exceptions whereby a few animals with relatively higher levels of $CD4^+$ T cells still developed AIDS while others exhibited low $CD4^+$ T cell numbers ($\leq$10% of baseline) with no obvious clinical signs of AIDS [14, 15, 36, 37] (Video 1: https://www.youtube.com/watch?v=g-RfAJyZsg0&t=23s and Video 2: https://www.youtube.com/watch?v=ynIom7fefxs&t=68s). Interestingly, while the number of monocytes in blood remained level, the percentage of recently dividing blood monocytes undergoing turnover, based on incorporation of BrdU administered 24 hours previously, drastically increased during terminal disease progression to AIDS in SIV-infected macaques [14, 25, 36–38]. To assess this observation further, machine learning algorithm modeling was applied to measure the relative contribution of covariates (singly or in combination) of monocyte turnover rate, percent $CD4^+$ T-cell loss, plasma viral levels, and viral strains to survival time or days until necropsy based on clinical AIDS criteria [15]. Matched time-point data sets were used (not imputed) and results from animals surviving to experimentally-timed endpoints were excluded. By Boosted Forest regression, monocyte turnover had the highest proportion of contribution to days until AIDS-associated necropsy (0.475 or 47.5%) followed by $CD4^+$ T-cell loss (0.216 or 21.6%), viral load (0.187 or 18.7%) or virus strain (below random) [15]. Classification categorization using decision tree algorithm modeling to analyze the flow chart-like proportion of the co-variates in predicting survival time in SIV-infected rhesus macaques further demonstrated that monocyte turnover (MTO) predicted a significantly shorter survival time among animals with $\geq$13.2% monocyte turnover rate followed by $CD4^+$ T cell decline. These results led to further investigations to delineate macrophage subpopulations and their roles in SIV/HIV infection pathogenesis.

6. Tissue macrophages in the pathogenesis of HIV/SIV infection

Increased monocyte turnover during terminal disease progression to AIDS suggested that monocytes and macrophages contribute to pathogenesis. While $CD4^+$ T cells are preferentially targeted by HIV/SIV, macrophages also become infected

with HIV/SIV, especially if a tissue contains few T cells (i.e. brain) or after $CD4^+$ T cell decline [19, 39, 40]. Infected macrophages are detected throughout the body [3, 4, 41–50]. Furthermore, resident macrophages infected with virus are resistant to apoptosis [17, 42, 51–53] and cytotoxic CD8 T cell lysis [54] thereby supporting their likely contribution to the virus reservoir.

a. **Lung.** In lung tissues and BAL fluids of rhesus macaques, two predominant populations of macrophages have been identified and characterized using in vivo administration of BrdU and dextran in conjunction with immunostaining methods to identify short-lived and long-lived macrophages, respectively [24]. Short-lived interstitial macrophages were relatively smaller in size, express CD163 (scavenger receptor) and primarily located in the lung interstitial tissue. Long-lived alveolar macrophages were relatively larger, double-positive (DP) for expressing both CD163 and CD206 (mannose receptor), and predominated in the alveolar spaces but also found in the interstitial tissue [24]. During terminal disease progression in SIV-infected rhesus macaques, the short-lived single-positive $CD163^+CD206^-$ macrophages in the interstitial lung tissues were readily infected and destroyed by SIV infection [25]. This loss in short-lived tissue macrophages may induce the increased production and turnover of monocytes to traffic and replace the damaged tissue macrophage that occurs during the transition from chronic to terminal disease progression after SIV infection. Furthermore, lung tissue lesions were progressively more severe with increasing monocyte turnover rates and macrophage accumulation (**Figure 1**) [25, 26]. Interestingly, resident long-lived double-positive $CD163^+CD206^+$ alveolar macrophages survived SIV infection despite efficacy in ART for reducing plasma viral loads to possibly become a virus reservoir [25]. In addition, while SIV-infected as well as uninfected $CD4^+$ T cells were killed in lungs of infected rhesus macaques, macrophages did

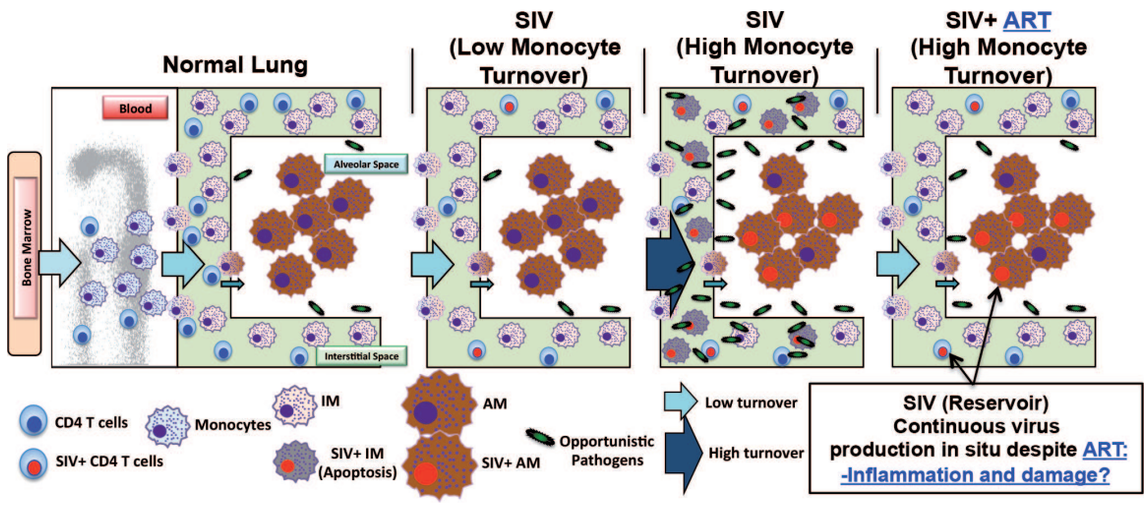

Figure 1.
Proposed mechanism of lung tissue damage in SIV-infected macaques undergoing ART. The lung contains at least two populations of macrophages; shorter-lived interstitial macrophages (IM) and longer-lived alveolar macrophages (AM). IM become massively infected with SIV and undergo a high rate of apoptosis that correlates with increased blood monocyte turnover. Conversely, SIV infection of the longer-lived AM does not lead to high rate of apoptosis compared to that of IM. ART appears to successfully block or inhibit SIV infection in IM but not in longer-lived AM. We thus expect that elimination of SIV-infected longer-lived AM, as well as SIV-infected $CD4^+$ T cells, is crucial to reduce inflammation and reverse pulmonary disease progression in SIV-infected aged macaques undergoing ART.

not decline and persisted, even if infected further indicating a population of long-lived macrophages that likely contribute to the virus reservoir [19].

b. **Brain**. Four populations of microglial, meningeal, choroid plexus, and peivascular macrophages exist in the brain [40, 55]. Resident microglial macrophages and macrophages of the meninges and choroid plexus exhibit low turnover rates and although infectable, are not major sites of HIV or SIV infection. Perivascular macrophages are located at the intersection between the central nervous system (CNS) and blood where systemic stimuli are encountered. These macrophages function in antigen presentation via MHC class II expression, exhibit a relatively higher turnover rate than parenchymal microglia during homeostasus, and are repopulated by peripheral monocytes that express $CD14^{high}CD16^{intermed}$ to then express CD206 and CD163 [56]. In SIV-infected macaques, perivascular macrophages that were replaced by trafficking infected monocytes establish CNS infection, whereas direct intrathecal injection with virus failed to produce brain infection [55, 57, 58]. The virus-infected perivascular macrophages were immunophenotypically similar to the trafficking activated ($CD16^+$) blood monocyte subsets and expressed CD163 [59]. Furthermore, increased monocyte turnover via BrdU kinetics, recruitment to brain, and accumulation of macrophages correlated with severity of encephalitis and neuronal injury in SIV-infected rhesus macaques. Encephalitic lesions were primarily comprised of myeloid cells including parenchymal macrophages, i.e. microglia, and perivascular macrophage cuffs, and macrophage accumulation better correlated with neurocognitive decline severity than did virus production [60, 61]. In addition, macrophage activation in relation to production of soluble CD163 (sCD163) in plasma and cerebral spinal fluid correlated with reduced neurocognition and virus levels further supporting macrophage contributions to SIV/HIV disease [38, 59, 61]. Macrophages of the brain could be reactivated to produce infectious virus using a virus outgrowth assay to also support their potential as a virus resevoir [41].

c. **Intestine**. The intestinal tract is a primary and early site of HIV/SIV infection that leads to massive depletion of intestinal $CD4^+$ T cells and high rate of viral replication [12]. The intestine also houses among the largest population of macrophages [62], and increased accumulation of intestinal macrophages was reported in HIV-positive patients [63] as well as in the ileum of SIV-infected rhesus macaques, especially during acute SIV infection and AIDS, but not during the chronic stage of infection [21]. The accumulated $CD163^+$ macrophages exhibited reduced phagocytic function that appeared to contribute to loss of intestinal integrity fueling further recruitment of macrophages in attempt to remove debris [64]. In rhesus macaques, two subsets of macrophages that comprised $CD163^+$ $CD206^+$ double-positive (DP) macrophages and $CD163^+$ $CD206^-$ single-positive (SP) macrophages were detected in the intestines using flow cytometry analyses [22]. In uninfected macaques, DP macrophages predominated over the SP macrophages. Forty-eight hours after BrdU administration, the majority of recently-dividing labeled cells were $CD163^+$ macrophages in the jejunum and colon in uninfected rhesus macaques that increased in SIV-infected animals [15]. Thus, monocytes appeared to migrate more rapidly from blood to intestine (lamina propria) during progression to AIDS.

DP macrophages predominated over SP macrophages in the lamina propria of uninfected rhesus macaques but SP macrophages were more common in the

lamina propria of SIV-infected animals with increased monocyte turnover. Interestingly, in the submucosa and muscular mucosa, DP macrophages were more frequent than SP macrophages in both infected and uninfected animals and there was a statistically significantly higher mean DP:SP macrophage ratio in the lamina propria of uninfected macaques compared to infected animals exhibiting higher monocyte turnover. In contrast, there were no significant differences in the submucosa DP:SP macrophage ratios of uninfected versus SIV-infected macaques with intermediate-to-higher monocyte turnover. Similar trends were observed for the DP:SP macrophage ratios in the jejunum of uninfected compared to infected animals with higher monocyte turnover [22]. This suggested that during terminal stages of SIV infection in animals with higher monocyte turnover, there was a loss in DP macrophages with concurrent increases in SP macrophages in the lamina propria, whereas submucosal DP and SP macrophage levels remained steady even after SIV infection and disease progression.

DP macrophages appeared to localize and remain primarily in the submucosa regardless of SIV infection status and appeared to comprise a long-lived macrophage population. This is relevant because long-lived (vs short-lived) macrophages would more likely serve as a virus reservoir, become dysregulated, and thereby contribute to chronic inflammation and pathogenesis. To explore this, we analyzed the distribution of colon macrophages that incorporated and retained the dextran (i.e. long-lived macrophages) relative to those that were labeled with thymidine analogues, BrdU or EdU (i.e. recently-dividing short-lived macrophages) [22]. $BrdU^+CD163^+$ macrophages were only in the lamina propria but not in the submucosa. Conversely, two months after dextran injection, $dextran^+CD163^+$ macrophages exclusively localized in the submucosa where there were ~ 10 times more DP macrophages than SP macrophages. These findings suggested DP macrophages in the submucosa are long-lived cells and that short-lived macrophages migrate from blood to lamina propria where they remain for shorter periods of time [22]. The presence of HIV-infected macrophages in human intestine and SIV-infected macrophages in rhesus macaque intestine supports the contribution of macrophages to gut pathogenesis and another tissue site of the virus reservoir [22, 23, 39].

d. **Heart.** In an early study characterizing heart tissues of rhesus macaques, macrophages were uniformly distributed throughout the heart in animals of all age groups ranging from infants to elderly adults, and were more prevalent than $CD3^+$ T cells and $CD20^+$ B cells [32]. Macrophages comprised approximately 2% of heart tissue cells in the younger animals and increased to a mean of nearly 4% in the older adults. $CD163^+$ macrophages predominated over $HAM56^+$ and $CD206^+$ macrophages, and were detected at significantly higher percentage in the older animals between 13 and 24 years of age as well as in heart tissues exhibiting severe histopathology or inflammation in animals of all age groups. In vivo dextran labeling and retention indicated that at least half of the macrophages were longer-lived in healthy adult heart tissues and may comprise the tissue-resident population of macrophages.

In heart tissues of SIV-infected rhesus macaques, increased numbers of $CD163^+$ macrophages were associated with pathology and fibrosis, and macrophages infected with SIV expressed CD163 with some also expressing HAM56 [65, 66].

In our studies of rhesus macaques, the majority of heart tissue macrophages were $CD163^+$ and long-lived (i.e. retained dextran), regardless of whether animals were chronically infected with or without ART [32] and Petkov et al., submitted]. Short-lived macrophages were rarely detected in the hearts of SIV-infected macaques at low monocyte turnover stage and of uninfected macaques with low histopathology scores [32]. In uninfected animals with higher histopathology scores (i.e. cardiac disease) or in SIV-infected animals with increased monocyte turnover, higher percentages of $BrdU^+$ short-lived macrophages were detected in heart suggesting infiltration of monocyte-derived short-lived macrophages during disease progression. Reduction in monocyte traffic to the heart of SIV-infected rhesus macaques via anti-alpha-4 integrin antibody reduced lesion severity in the heart and decreased levels of $CD163^+CD68^+$ macrophages, implicating accumulation of short-lived macrophages as a promoter of SIV-associated heart disease [67]. Unpublished results from our lab suggested that the level of long-lived macrophage infection also influences the dynamics and recruitment of short-lived macrophages related to heart tissue damage during HIV infection. In addition, HIV and SIV infections appear to accelerate biological aging based on increased or earlier onset of chronic inflammatory diseases, including CVD [68–75]. Cellularity of heart tissues declined with age in rhesus macaques [32] and there also was a reduction in heart tissue cellularity in SIV-infected younger adult macaques similar to that in uninfected older animals. Thus an increase in macrophages relative to tissue cellularity may contribute to loss of tissue homeostasis during natural aging and SIV/HIV-associated accelerated aging.

e. **Adipose tissue.** Tissue macrophages also constitute a major portion of the immune cell population in adipose [76–78]. Macrophages in subcutaneous adipose tissue of rhesus macaques and humans expressed CD68 and predominated over T cells and B cells [79]. CD68 was heavily expressed on cells of the monocyte and macrophage lineage [80] along with CD163 and CD206 that appear to reflect 'anti-inflammatory' macrophages [81, 82]. In subcutaneous adipose tissue of rhesus macaques, there were at least two major macrophage subsets. $CD68^+CD163^+CD206^+$ macrophages were more common than the $CD68^+CD163^-CD206^-$ macrophages, suggesting the predominant population exhibited an 'anti-inflammatory' phenotype. While triple-positive adipose tissue macrophages were found throughout the tissue, $CD68^+CD163^-CD206^-$ were mainly detected inside crown-like structures and interstitial clusters, intimating these macrophages may be associated with pathology and inflammation [79]. As also observed in heart tissue macrophages, the vast majority of subcutaneous adipose tissue macrophages in rhesus macaques were longer-living (i.e. retained in vivo administered dextran) [32, 79]. These longer-lived subcutaneous adipose macrophages co-expressed CD68, CD163, and CD206. The $CD68^+$ macrophages that did not contain dextran were generally found in the crown-like structure and interstitial spaces, and also were negative for CD163 and CD206. A small but distinct subpopulation of these macrophages simultaneously expressed Ki67 in their nuclei, located to the crown-like structure and interstitial clusters, but also to the interstitial spaces, suggesting that they were self-renewing at the time of sampling. Though only a small proportion of macrophages were self-renewing at any one time, these observations provide evidence that, like in mice, adipose tissue macrophages from rhesus macaques are predominantly long-lived and may self-maintain in tissue via slow local proliferation.

Adipose tissue macrophages also have provided evidence that $CD14^+$ adipose tissue macrophages become infected with HIV and simian immunodeficiency virus (SIV) [45]. During SIV infection of cynomolgus macaques, subcutaneous macrophages also exhibited a pro-inflammatory phenotype expressing CD14 but not CD163 or CD206 [83] thereby contributing to the chronic inflammation often observed during SIV/HIV infection.

7. Future goals: targeting macrophages to reduce pathogenesis

Macrophages regulate inflammation and contribute to the SIV/HIV reservoir, thereby affecting pathogenesis of infection. Two general approaches have been applied experimentally to target macrophages in macaques that may benefit treatments for HIV. Bisphosphonates have been used for treating osteoporosis and other bone diseases, and target bone macrophages or osteoclasts to inhibit bone resorption [84]. In rhesus and cynomologus macaques, liposome-encapsulated alendronate administered intravenously reduced levels of $CD14^+CD16^-$ and $CD14^-CD16^+$ monocytes as well as $CD163^+$ tissue macrophages with relatively low or no toxicity [85]. Liposome-clodronate inoculated intracisternally selectively depleted $CD206^+$ perivascular macrophages of the brain as well as $CD14^+$ monocytes in SIV-infected rhesus macaques [56]. A second approach was to apply natalizumab, an antibody to α-4-integrin that inhibits monocyte/macrophage trafficking. This antibody reduced neuropathology and cardiac pathology in SIV-infected rhesus macaques [56, 67]. Increasing evidence for the presence of SIV/HIV-infected and persistent macrophage reservoirs supports further studies and approaches for modulating or targeting macrophages to achieve cure.

Acknowledgements

The authors gratefully acknowledge research funding from the National Institutes of Health (grants AI097059, AI110163, and MH108458, to M.J.K., AG052349 to E.S.D., HL139278 to E.S.D. and M.J.K., OD011104, OD010568, and OD024282 to the Tulane National Primate Research Center and OD011107 to the California National Primate Research Center).

Author contributions

E.S.D. and M.J.K. conceived and wrote the manuscript.

Declaration of interest

The authors declare no competing interests.

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References

[1] DiNapoli SR, Hirsch VM, Brenchley JM. Macrophages in progressive human immunodeficiency virus/Simian immunodeficiency virus infections. Journal of Virology. 2016;**90**(17):7596-7606

[2] Gordon S, Plüddemann A. The mononuclear phagocytic system. generation of diversity. Frontiers in Immunology. 2019;**10**(1893):1-10

[3] Kruize Z, Kootstra NA. The role of macrophages in HIV-1 persistence and pathogenesis. Front Microbiology. 2019;**10**:2828

[4] Khanal S, Schank M, El Gazzar M, Moorman JP, Yao ZQ. HIV-1 latency and viral reservoirs: Existing reversal approaches and potential technologies, targets, and pathways involved in HIV latency studies. Cells. 2021;**10**(2):1-23

[5] Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Natural Review Immunology. 2008;**8**(12):958-969

[6] Murray PJ. Macrophage polarization. Annual Review of Physiology. 2017;**79**:541-566

[7] Ross EA, Devitt A, Johnson JR. Macrophages: The good, the bad, and the gluttony. Frontiers in Immunology. 2021;**12**:708186

[8] Didier ES, MacLean AG, Mohan M, Didier PJ, Lackner AA, Kuroda MJ. Contributions of nonhuman primates to research on aging. Veterinary Pathology. 2016;**53**(2):277-290

[9] Goulder P, Deeks SG. HIV control: Is getting there the same as staying there? PLoS Pathogens. 2018;**14**(11):e1007222

[10] Martins MA, Watkins DI. What is the predictive value of animal models for vaccine efficacy in humans? Rigorous Simian immunodeficiency virus vaccine trials can be instructive. Cold Spring Harbor Perspectives in Biology. 2018;**10**(4):1-10

[11] Williams K, Lackner A, Mallard J. Non-human primate models of SIV infection and CNS neuropathology. Current Opinion in Virology. 2016;**19**:92-98

[12] Veazey RS, DeMaria M, Chalifoux LV, Shvetz DE, Pauley DR, Knight HL, et al. Gastrointestinal tract as a major site of $CD4^+$ T cell depletion and viral replication in SIV infection. Science (New York, NY). 1998;**280**(5362):427-431

[13] Evans DT, Silvestri G. Nonhuman primate models in AIDS research. Current Opinion in HIV and AIDS. 2013;**8**(4):255-261

[14] Hasegawa A, Liu H, Ling B, Borda JT, Alvarez X, Sugimoto C, et al. The level of monocyte turnover predicts disease progression in the macaque model of AIDS. Blood. 2009;**114**(14):2917-2925

[15] Takahashi N, Ardeshir A, Holder GE, Cai Y, Sugimoto C, Mori K, et al. Comparison of predictors for terminal disease progression in simian immunodeficiency virus/simian-HIV-infected rhesus macaques. AIDS (London, England). 2021;**35**(7):1021-1029

[16] Pathai S, Bajillan H, Landay AL, High KP. Is HIV a model of accelerated or accentuated aging? The Journals of Gerontology Series A, Biological Sciences and Medical Sciences. 2014;**69**(7):833-842

[17] Abbas W, Tariq M, Iqbal M, Kumar A, Herbein G. Eradication of HIV-1 from the macrophage reservoir: An uncertain goal? Viruses. 2015;**7**(4):1578-1598

[18] Clayton KL, Garcia JV, Clements JE, Walker BD. HIV infection of macrophages: Implications for pathogenesis and cure. Pathogens & Immunity. 2017;**2**(2):179-192

[19] Li Y, Kang G, Duan L, Lu W, Katze MG, Lewis MG, et al. SIV infection of lung macrophages. PloS One. 2015;**10**(5):e0125500

[20] Micci L, Alvarez X, Iriele RI, Ortiz AM, Ryan ES, McGary CS, et al. $CD4^+$ depletion in SIV-infected macaques results in macrophage and microglia infection with rapid turnover of infected cells. PLoS Pathogens. 2014;**10**(10):e1004467

[21] Swan ZD, Wonderlich ER, Barratt-Boyes SM. Macrophage accumulation in gut mucosa differentiates AIDS from chronic SIV infection in rhesus macaques. European Journal of Immunology. 2016;**46**(2):446-454

[22] Takahashi N, Sugimoto C, Allers C, Alvarez X, Kim WK, Didier ES, et al. Shifting dynamics of intestinal macrophages during Simian immunodeficiency virus infection in adult rhesus macaques. Journal of Immunology (Baltimore, Md : 1950). 2019;**202**(9):2682-2689

[23] Zalar A, Figueroa MI, Ruibal-Ares B, Baré P, Cahn P, de Bracco MM, et al. Macrophage HIV-1 infection in duodenal tissue of patients on long term HAART. Antiviral Research. 2010;**87**(2):269-271

[24] Cai Y, Sugimoto C, Arainga M, Alvarez X, Didier ES, Kuroda MJ. In vivo characterization of alveolar and interstitial lung macrophages in rhesus macaques: Implications for understanding lung disease in humans. Journal of Immunology (Baltimore, Md : 1950). 2014;**192**(6):2821-2829

[25] Cai Y, Sugimoto C, Arainga M, Midkiff CC, Liu DX, Alvarez X, et al. Preferential destruction of interstitial macrophages over alveolar macrophages as a cause of pulmonary disease in Simian immunodeficiency virus-infected rhesus macaques. Journal of Immunology (Baltimore, Md : 1950). 2015;**195**(10):4884-4891

[26] Cai Y, Sugimoto C, Liu DX, Midkiff CC, Alvarez X, Lackner AA, et al. Increased monocyte turnover is associated with interstitial macrophage accumulation and pulmonary tissue damage in SIV-infected rhesus macaques. Journal of Leukocyte Biology. 2015;**97**(6):1147-1153

[27] Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, et al. Macrophage plasticity, polarization, and function in health and disease. Journal of Cellular Physiology. 2018;**233**(9):6425-6440

[28] Röszer T. Understanding the biology of self-renewing macrophages. Cells. 2018;**7**(8):1-21

[29] Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, et al. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity. 2013;**38**(4):792-804

[30] Takahashi N, Ardeshir A, Holder GE, Cai Y, Sugimoto C, Mori K, et al. Comparison of predictors for terminal disease progression in SIV/

SHIV-infected rhesus macaques. AIDS (London, England). 2021;**35**:1021-1029

[31] Solius GM, Maltsev DI, Belousov VV, Podgorny OV. Recent advances in nucleotide analogue-based techniques for tracking dividing stem cells: An overview. Journal of Biological Chemistry. 2021;**297**(5):101345

[32] Petkov DI, Liu DX, Allers C, Didier PJ, Didier ES, Kuroda MJ. Characterization of heart macrophages in rhesus macaques as a model to study cardiovascular disease in humans. Journal of Leukocyte Biology. 2019;**106**(6):1241-1255

[33] Veazey R, Lackner A. The mucosal immune system and HIV-1 infection. AIDS R. 2003;**5**(4):245-252

[34] Pandrea I, Silvestri G, Apetrei C. AIDS in african nonhuman primate hosts of SIVs: A new paradigm of SIV infection. Current HIV Research. 2009;**7**(1):57-72

[35] Doitsh G, Greene WC. Dissecting how $CD4^+$ T cells are lost during HIV infection. Cell Host & Microbe. 2016;**19**(3):280-291

[36] Kuroda MJ. Macrophages: Do they impact AIDS progression more than $CD4^+$ T cells? Journal of Leukocyte Biology. 2010;**87**(4):569-573

[37] Kim WK, McGary CM, Holder GE, Filipowicz AR, Kim MM, Beydoun HA, et al. Increased expression of CD169 on blood monocytes and its regulation by virus and CD8 T cells in macaque models of HIV infection and AIDS. AIDS Research and Human Retroviruses. 2015;**31**(7):696-706

[38] Burdo TH, Soulas C, Orzechowski K, Button J, Krishnan A, Sugimoto C, et al. Increased monocyte turnover from bone marrow correlates with severity of SIV encephalitis and CD163 levels in plasma. PLoS Pathogens. 2010;**6**(4):e1000842

[39] Pahar B, Kuebler D, Rasmussen T, Wang X, Srivastav SK, Das A, et al. Quantification of viral RNA and DNA positive cells in tissues from Simian immunodeficiency virus/Simian human immunodeficiency virus infected controller and progressor rhesus macaques. Frontiers in Microbiology. 2019;**10**:2933

[40] Kim W-K, Corey S, Alvarez X, Williams K. Monocyte/macrophage traffic in HIV and SIV encephalitis. Journal of Leukocyte Biology. 2003;**74**(5):650-656

[41] Abreu C, Shirk EN, Queen SE, Beck SE, Mangus LM, Pate KAM, et al. Brain macrophages harbor latent, infectious simian immunodeficiency virus. AIDS (London, England). 2019;**33**(Suppl. 2):S181-S1s8

[42] Abreu CM, Veenhuis RT, Avalos CR, Graham S, Parrilla DR, Ferreira EA, et al. Myeloid and $CD4^+$ T cells comprise the latent reservoir in antiretroviral therapy-suppressed SIVmac251-infected macaques. mBio. 2019;**10**(4):1-19

[43] Aggarwal A, McAllery S, Turville SG. Revising the role of myeloid cells in HIV pathogenesis. Current HIV/AIDS Reports. 2013;**10**(1):3-11

[44] Arainga M, Edagwa B, Mosley RL, Poluektova LY, Gorantla S, Gendelman HE. A mature macrophage is a principal HIV-1 cellular reservoir in humanized mice after treatment with long acting antiretroviral therapy. Retrovirology. 2017;**14**(1):17

[45] Damouche A, Lazure T, Avettand-Fenoel V, Huot N, Dejucq-Rainsford N, Satie AP, et al.

Adipose tissue is a neglected viral reservoir and an inflammatory site during chronic HIV and SIV infection. PLoS Pathogens. 2015;**11**(9):e1005153

[46] Freed EO, Martin MA. HIV-1 infection of non-dividing cells. Nature. 1994;**369**(6476):107-108

[47] Hassan J, Browne K, De Gascun C. HIV-1 in monocytes and macrophages: An overlooked reservoir? Viral Immunology. 2016;**29**(9):532-533

[48] Mitchell BI, Laws EI, Ndhlovu LC. Impact of myeloid reservoirs in HIV cure trials. Current HIV/AIDS Reports. 2019;**16**(2):129-140

[49] Pallikkuth S, Mohan M. Adipose tissue: Sanctuary for HIV/SIV persistence and replication. Trends in Microbiology. 2015;**23**(12):748-750

[50] Sharifi HJ, Furuya AM, de Noronha CM. The role of HIV-1 Vpr in promoting the infection of nondividing cells and in cell cycle arrest. Current Opinion in HIV and AIDS. 2012;**7**(2):187-194

[51] Busca A, Saxena M, Kryworuchko M, Kumar A. Anti-apoptotic genes in the survival of monocytic cells during infection. Current Genomics. 2009;**10**(5):306-317

[52] Honeycutt JB, Wahl A, Baker C, Spagnuolo RA, Foster J, Zakharova O, et al. Macrophages sustain HIV replication in vivo independently of T cells. The Journal of Clinical Investigation. 2016;**126**(4):1353-1366

[53] Malim MH, Bieniasz PD. HIV restriction factors and mechanisms of evasion. Cold Spring Harbor Perspectives in Medicine. 2012;**2**(5):a006940

[54] Cribbs SK, Lennox J, Caliendo AM, Brown LA, Guidot DM. Healthy HIV-1-infected individuals on highly active antiretroviral therapy harbor HIV-1 in their alveolar macrophages. AIDS Research Human Retroviruses. 2015;**31**(1):64-70

[55] Kim WK, Avarez X, Williams K. The role of monocytes and perivascular macrophages in HIV and SIV neuropathogenesis: Information from non-human primate models. Neurotoxicity Research. 2005;**8**(1-2):107-115

[56] Holder GE, McGary CM, Johnson EM, Zheng R, John VT, Sugimoto C, et al. Expression of the mannose receptor CD206 in HIV and SIV encephalitis: A phenotypic switch of brain perivascular macrophages with virus infection. Journal of Neuroimmune Pharmacology: The Official Journal of the Society on NeuroImmune Pharmacology. 2014;**9**(5):716-726

[57] Hurtrel B, Chakrabarti L, Hurtrel M, Montagnier L. Target cells during early SIV encephalopathy. Research Virology. 1993;**144**(1):41-46

[58] Smith MS, Niu Y, Li Z, Adany I, Pinson DM, Liu ZQ, et al. Systemic infection and limited replication of SHIV vaccine virus in brains of macaques inoculated intracerebrally with infectious viral DNA. Virology. 2002;**301**(1):130-135

[59] Fischer T, Wyatt CM, D'Agati VD, Croul S, McCourt L, Morgello S, et al. Mononuclear phagocyte accumulation in visceral tissue in HIV encephalitis: Evidence for increased monocyte/macrophage trafficking and altered differentiation. Current HIV Research. 2014;**12**(3):201-212

[60] Williams KC, Corey S, Westmoreland SV, Pauley D, Knight H, deBakker C, et al. Perivascular

macrophages are the primary cell type productively infected by simian immunodeficiency virus in the brains of macaques: Implications for the neuropathogenesis of AIDS. The Journal of Experimental Medicine. 2001;**193**(8):905-915

[61] Williams K, Burdo TH. Monocyte mobilization, activation markers, and unique macrophage populations in the brain: Observations from SIV infected monkeys are informative with regard to pathogenic mechanisms of HIV infection in humans. Journal of Neuroimmune Pharmacology : The Official Journal of the Society on NeuroImmune Pharmacology. 2012;**7**(2):363-371

[62] Lee SH, Starkey PM, Gordon S. Quantitative analysis of total macrophage content in adult mouse tissues. Immunochemical studies with monoclonal antibody F4/80. The Journal of Experimental Medicine. 1985;**161**(3):475-489

[63] Allers K, Fehr M, Conrad K, Epple HJ, Schurmann D, Geelhaar-Karsch A, et al. Macrophages accumulate in the gut mucosa of untreated HIV-infected patients. The Journal of Infectious Diseases. 2014;**209**(5):739-748

[64] Swan ZD, Bouwer AL, Wonderlich ER, Barratt-Boyes SM. Persistent accumulation of gut macrophages with impaired phagocytic function correlates with SIV disease progression in macaques. European Journal of Immunology. 2017;**47**(11):1925-1935

[65] Yearley JH, Pearson C, Shannon RP, Mansfield KG. Phenotypic variation in myocardial macrophage populations suggests a role for macrophage activation in SIV-associated cardiac disease. AIDS Research Human Retroviruses. 2007;**23**(4):515-524

[66] Walker JA, Sulciner ML, Nowicki KD, Miller AD, Burdo TH, Williams KC. Elevated numbers of $CD163^+$ macrophages in hearts of simian immunodeficiency virus-infected monkeys correlate with cardiac pathology and fibrosis. AIDS Research Human Retroviruses. 2014;**30**(7):685-694

[67] Walker JA, Beck GA, Campbell JH, Miller AD, Burdo TH, Williams KC. Anti-α4 integrin antibody blocks monocyte/macrophage traffic to the heart and decreases cardiac pathology in a SIV infection model of AIDS. Journal of the American Heart Association. 2015;**4**(7):1-11

[68] Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annual Review Medicine. 2011;**62**:141-155

[69] Deeks SG, Verdin E, McCune JM. Immunosenescence and HIV. Current Opinion in Immunology. 2012;**24**(4):501-506

[70] High KP, Brennan-Ing M, Clifford DB, Cohen MH, Currier J, Deeks SG, et al. HIV and aging: State of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. Journal of Acquired Immune Deficiency Syndrome. 2012;**60**(Suppl. 1):S1-S18

[71] Pathai S, Lawn SD, Gilbert CE, McGuinness D, McGlynn L, Weiss HA, et al. Accelerated biological ageing in HIV-infected individuals in South Africa: A case-control study. AIDS (London, England). 2013;**27**(15):2375-2384

[72] Herskowitz A, Willoughby S, Wu TC, Beschorner WE, Neumann DA, Rose NR, et al. Immunopathogenesis of HIV-1-associated cardiomyopathy. Clinical Immunology and Immunopathology. 1993;**68**(2):234-241

[73] Ho JE, Hsue PY. Cardiovascular manifestations of HIV infection. Heart (British Cardiac Society). 2009;**95**(14):1193-1202

[74] Sani MU. Myocardial disease in human immunodeficiency virus (HIV) infection: A review. Wiener Klinische Wochenschrift. 2008;**120**(3-4):77-87

[75] Zareba KM, Lipshultz SE. Cardiovascular complications in patients with HIV infection. Current Infectious Disease Reports. 2003;**5**(6):513-520

[76] Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, et al. $CD8^+$ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nature Medicine. 2009;**15**(8):914-920

[77] Onodera T, Fukuhara A, Shin J, Hayakawa T, Otsuki M, Shimomura I. Eicosapentaenoic acid and 5-HEPE enhance macrophage-mediated Treg induction in mice. Scientific Reports. 2017;**7**(1):4560

[78] Wang L, Liu J, Zhang A, Cheng P, Zhang X, Lv S, et al. BVT.2733, a selective 11beta-hydroxysteroid dehydrogenase type 1 inhibitor, attenuates obesity and inflammation in diet-induced obese mice. PloS One. 2012;**7**(7):e40056

[79] Fahlberg M. The impact of Simian immunodeficiency virus on subcutaneous adipose tissue of rhesus macaues. Tulane University Theses and Dissertation Archive. 2018. https://digitallibrary.tulane.edu/islandora/object/tulane%3A110475

[80] Martinez-Pomares L, Platt N, McKnight AJ, da Silva RP, Gordon S. Macrophage membrane molecules: Markers of tissue differentiation and heterogeneity. Immunobiology. 1996;**195**(4-5):407-416

[81] Fabriek BO, Dijkstra CD, van den Berg TK. The macrophage scavenger receptor CD163. Immunobiology. 2005;**210**(2-4):153-160

[82] Stein M, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: A marker of alternative immunologic macrophage activation. The Journal of Experimental Medicine. 1992;**176**(1):287-292

[83] Pallikkuth S, Mohan M. Adipose tissue: Sanctuary for HIV/SIV persistence and replication. Trends in Microbiology. 2015;**23**(12):748-750

[84] Kuźnik A, Październiok-Holewa A, Jewula P, Kuźnik N. Bisphosphonates-much more than only drugs for bone diseases. European Journal of Pharmacology. 2020;**866**:172773

[85] Burwitz BJ, Reed JS, Hammond KB, Ohme MA, Planer SL, Legasse AW, et al. Technical advance: Liposomal alendronate depletes monocytes and macrophages in the nonhuman primate model of human disease. Journal of Leukocyte Biology. 2014;**96**(3):491-501