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GUEST COMMENTARY

Editor's Commentary for Special Issue: "The Role of Macrophages in HIV Persistence"

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Abstract
Macrophages as reservoirs for persistent HIV infection has gained renewed importance, with an intense research focus dedicated to eradication strategies. Clearance of both latent and productive HIV from these important reservoirs is essential for successful eradication. This spe cial theme issue contains 11 papers, including 6 Invited Reviews, 1 Brief Report and 4 Original Articles, that focus on the various aspects of the macrophage as pertains to HIV persistence, latency and cure. These topics include: functional latency of macrophages and microglia, the link between peripheral monocytes and pathogenesis, macrophages as sources of HIV RNA and DNA in virally suppressed patients, brain imaging of neuroinflammation, macrophages as drug delivery vehicles, therapeutic strategies of infected macrophages for cure, and the role of drugs of abuse in enhancing macrophage viral persistence.

Keywords HIV · Macrophage · Reservoir · Latency

Persistence of viral reservoirs in the peripheral blood, lymphoid tissues and brain remains a hurdle to complete eradication of virus and to cure the infection. HIV establishes a latent reservoir in the memory T cell population (McGary et al. 2017), with residual virus production in the gut, and other lymphoid tissues (Estes et al. 2017; Deleage et al. 2016), despite antiretroviral therapy (ART). Establishment of reservoirs may contribute to viral persistence and provide important additional sources for rebound following treatment interruption. There is strong evidence to support that microglia and macrophages can be productively infected thereby serving as cellular reservoirs, which are broadly defined as all infected cells and tissues that contain any form of HIV persistence contributing to HIV pathogenesis. Key viral sanctuaries are well characterized, all of which contain cells of the myeloid lineage, including peripheral blood, genitourinary tract, adipose tissue (stromal vascular fraction), gastrointestinal tract, gastrointestinal-associated lymphatic tissue (GALT), lymph nodes, parenchymal organs (lungs, liver, spleen) and brain. Within these sanctuaries, macrophages can support active viral replication and establish viral reservoirs.

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Whether macrophages can support HIV latency similar to memory T cells is still debated. There have been extensive studies on the establishment of latency in CD4+ T cells, however, less is known about whether HIV establishes latency in myeloid cells and microglia. Simian immunodeficiency virus (SIV) models have produced robust evidence for the persistence of SIV DNA in myeloid cells, even after prolonged suppression of viral replication with ART (Zink et al. 2010). However, detection of viral RNA and DNA in macrophages is not indicative of the cell's capacity to produce replication component virus. Work by Clements and colleagues has demonstrated that microglia from SIV-infected monkeys contain viral RNA and DNA. Using a novel quantitative viral outgrowth assay (QVOA), they showed that brain macrophages are replication competent and capable of re-establishing productive infection upon ART interruption. Her group has provided an outstanding review in this special issue entitled "*A Quantitative Approach to SIV Functional Latency in Brain Macrophages*" (Abreu et al. 2018).

The role of microglial infection in long-term HIV latency and persistence remains controversial, despite HIV DNA detection in post-mortem brain of ART suppressed individuals and studies in SIV-infected monkeys. In this context however, Dr. Karn has developed a model of latency in microglia derived from human brain cortex. In this special issue, his group presents data in an original article, "*The Glucocorticoid Receptor is a Critical Regulator of HIV Latency in Human Microglial Cells*" (Alvarez-Carbonell et al. 2018). They demonstrate that addition of dexamethasone (DEXA), a glucocorticoid receptor (GR) agonist and an anti-inflammation mediator silenced the HIV provirus. DEXA represses the expression of inflammatory gene products including IL-1β and TNF-α, thereby placing the cells in a latent state. In these studies, the GR agonist was capable of long-term HIV silencing in microglia by direct association with the HIV LTR promoter.

Dr. Ances provides an excellent review of current techniques in brain imaging for detection of neuroinflammation in his review, "*Molecular Imaging of Neuroinflammation in HIV*" (Boerwinkle and Ances 2018). Due to the difficulty of repeatedly evaluating the brain in vivo using invasive approaches, neuroimaging techniques provide a non-invasive and direct method to assess changes in the brain. Positron emission tomography (PET) can be used to observe cells of interest through tracer compounds, and of specific interest for the brain, translocator protein (TSPO) localizes to microglia by binding benzodiazepine. In HIV neuroimaging, TSPO has only been used in a few published studies (Alvarez-Carbonell et al. 2018) and the data vary due to different ligands used and sample sizes. To date, there are no specific markers for specific virally infected cells in vivo. Development of additional ligands, as well as, improved methods for longitudinal studies are needed for future implementation of PET imaging in HIV neuroinflammation.

Numerous publications in this special issue highlight how macrophages provide suitable viral reservoirs and are directly involved in viral persistence. The review, "*Host and Viral Factors Influencing Interplay Between the Macrophage and HIV-1*" (Machado Andrade and Stevenson 2018), by Dr. Stevenson nicely details the types of macrophages important in HIV infection, mechanisms imposed by the cellular immune response to eliminate virus from infected cells and mechanisms that make macrophages candidates for HIV persistence. His review points out that macrophages are long-lived cells and are resistant to cytopathic effects of HIV, as macrophages allow transport of the viral core to an intact nucleus, integration of viral DNA into transcriptionally active sites on host chromosomes, and harbor proviral DNA that upon reactivation generates replication component virus. In this way, macrophages can act as latent viral reservoirs even without active viral replication. While viral reactivation from macrophages has been shown in animal models, macrophages as a lasting HIV sanctuary is difficult to show in HIV/ART suppressed people.

Ko et al in the original article "*Macrophages but not astrocytes harbor HIV DNA in the brains of HIV-1-infected aviremic individuals on suppressive antiretroviral therapy*" *(Ko* et al. 2018*)* set out to uncover whether HIV could be detected in the brains of individuals on long-term suppressive ART and to determine the cellular basis for the persistence of HIV in the brain. Using a highly sensitive RNA and DNAscope technique to detect low copy viral RNA and DNA, they consistently detected HIV DNA in macrophage and microglia, but not in astrocytes in brains from long-term virally suppressed people with HIV. However, the absence of evidence for HIV DNA in astrocytes by these studies does not mean that other groups may detect HIV DNA+ astrocytes. For some, active infection of astrocytes remains very controversial, yet there are no publications to date that show convincing evidence of astrocyte infection in individuals on suppressive ART.

Dr. Berman contributes an original manuscript "*CCR2 on peripheral blood CD14+CD16+ monocytes correlate with neuronal damage, HIV-associated neurocognitive disorders, and peripheral HIV DNA: reseeding of CNS reservoirs?*" (Veenstra et al. 2018). Monocytes, myeloid cells in the peripheral blood, can transmit the virus to and from anatomic sites, importantly the gut and brain. Previous work has shown that monocytes are critical vectors for viral entry into tissues during early infection, and that they play a central role in the development and persistence of HIV in various tissues, including in the brain (Campbell et al. 2014; Burdo et al. 2013). Early studies showed that increased CD14 + CD16+ monocytes and the presence of HIV DNA in monocytes correlated to brain pathology (Pulliam et al. 1997; Fischer-Smith et al. 2001; Fischer-Smith et al. 2008; Shiramizu et al. 2005; Ancuta et al. 2008); chemokine ligand 2 (CCL2) increased monocyte migration to the brain, providing a plausible mechanism of seeding CNS with virus (Williams et al. 2013); and the chemokine receptor CCR2/CCL2 axis plays a role in leukocyte recruitment and sustaining inflammatory status, both of which are hallmarks of post-ART HIV infection (Covino et al. 2016). Previous data from Dr. Berman indicate that HIV infection of monocytes in concert with CCL2-driven chemotaxis causes increased transmigration of monocytes across an in vitro model of the blood brain barrier (BBB) (Williams et al. 2013; Eugenin et al. 2006). Here, they extend those studies to show that the presence of CCR2 on CD14 + CD16+ inflammatory monocytes is associated with neuronal damag and CCR2 on CD14 + CD16+ inflammatory monocytes relates to HIV DNA in PBMCs. These data demonstrate a link among peripheral monocytes, viral DNA and neuronal damage.

Drugs of abuse have an effect on macrophage infection and activation, and two original publications focus on the effect of drugs of abuse on monocytes and macrophages in the context of HIV. The first, an article by Gaskill and colleagues, "*Role of macrophage dopamine receptors in mediating cytokine production: Implications for neuroinflammation in the context of HIV-associated neurocognitive disorders*" (Nolan et al. 2018) builds on previous work showing that dopamine increased HIV infection in macrophages. Here, they present data showing that dopamine treatment of macrophages from people with HIV on ART promotes inflammation. The second, a brief report by Carrico and colleagues, "*Psychosocial Correlates of Monocyte Activation and HIV persistence in Methamphetamine Users*" (Grosgebauer et al. 2018) examined a cohort of HIV+ methamphetamine users undergoing treatment. They showed that psychosocial factors relevant to recovery from substance abuse were associated with lower monocyte activation and decreased HIV DNA, likely contributing to decreased substance use.

Two review articles focused on therapeutic strategies and drug delivery to macrophage reservoirs: "*Broad spectrum mixed lineage kinase type 3 inhibition and HIV-1 persistence in macrophages*" (Saminathan et al. 2019) by Dr. Gelbard and colleagues, and "*HIV and the Macrophage: From Cell Reservoirs to Drug Delivery to Viral Eradication*" (Herskovitz and Gendelman 2018) by Drs. Herskovitz and Gendelman. Not only are macrophages important for viral replication and inflammation during HIV infection, but macrophages can also act as cellular carriages for nanoparticles, due to their high cytoplasmic content. Macrophages can deliver treatments and diagnostic particles to privileged areas that harbor HIV that conventional therapies cannot access. Macrophages can be used to improve methods of drug delivery by extending the half-life and improving drug delivery to HIV reservoirs. Dr. Gelbard presents data using a mixed lineage kinase inhibitor, URMC-099, to restore autophagy as a therapeutic response in persistently infected macrophage in combination with nanoformulated ART. The nanoformulation ART is a long-acting slow effective release (LASER) ART, developed by the Gendelman laboratory, which takes advantage of macrophage phagocytosis to contain drugs and simultaneously take advantage of the inflammatory environment to deliver ART to reservoirs.

Macrophages as a reservoir for persistent HIV infection has recently regained attention, with an intense research focus dedicated to eradication strategies. Both the review from Dr. Gendelman and a review from Drs. Peterson and MacLean, "*Current and Future Therapeutic Strategies for Lentiviral Eradication from Macrophage Reservoirs*" (Peterson and MacLean 2018), discuss the importance of targeting macrophage reservoirs in cure strategies, as clearance of both latent and productive HIV from the brain are essential for successful eradication. Traditional ART has helped reduced AIDS-related morbidity and mortality, but viral persistence remains where traditional ART is not as effective. Therefore, additional strategies are needed for permanent removal of HIV from the host genome. Gene editing of viral genes and cellular targets are actively being explored as novel methods of HIV eradication.

In summary, taken together, works in this theme issue conclude that monocytes/macrophages warrant recognition as persistent and latent reservoirs of HIV/SIV in the presence of ART. Sources of both systemic and brain inflammation are important targets for HIV eradication, with particular interest in myeloid cells. The promising use of macrophages as vehicles of drug transport and therapeutic delivery provides an opportunity to target reservoirs at privileged sites. In the post-ART era, novel strategies are needed to target removal of HIV through genetic engineering technologies, where traditional T cell targeted ART should be combined with adjunctive macrophage-specific targeting therapeutics, Moreover, non-invasive technologies should be improved upon to better detect and understand viral reservoirs in people with HIV.

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Compliance with Ethical Standards

Conflict of Interest The author declares no conflict of interest.

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