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Adipose Tissue: Sanctuary for HIV/SIV Persistence and Replication

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Abstract

This commentary highlights new findings from a recent study identifying adipose tissue as a potential HIV reservoir and a major site of inflammation during chronic human/simian immunodeficiency virus (HIV/SIV) infection. A concise discussion about upcoming challenges and new research avenues for reducing chronic adipose inflammation during HIV/SIV infection is presented.

Keywords

HIV/SIV reservoir; adipose tissue; CD4/CD8 T-cell; macrophage; inflammation

Antiretroviral therapy (ART) during HIV infection effectively reduces viremia, allows immune reconstitution and has increased the lifespan of HIV-infected individuals. Nevertheless, complete eradication of HIV-1 remains an unresolved task due to the persistence of long-lived viral reservoirs in different anatomical compartments coupled with the largely unknown nature of the extent and magnitude of these viral sanctuaries [1–2]. Accordingly, studies providing insights into HIV cellular reservoirs in previously unexplored anatomical compartments, and their contribution to HIV pathogenesis have great relevance for defining novel therapeutic strategies to achieve the goals of HIV cure. In this context, a recent study by Damouche and colleagues published in the September 2015 issue of *PLoS Pathogens* has extensively addressed the contribution of adipose tissue to maintenance of viral reservoirs and as a site of persistent inflammation during chronic HIV/SIV infection [3].

Adipose tissue is an immunologically dynamic compartment consisting of resident CD4 and CD8 T cells, T regulatory (T_{REG}) cells, NK cells, B cells, and macrophages within the stromal vascular fraction (SVF) that perform important immune and inflammatory functions

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[4]. To demonstrate infection of adipose immune cells, the authors analyzed both subcutaneous adipose tissue (SCAT) and visceral adipose tissue (VAT) from chronically SIV-infected cynomolgus macaques [3]. Viremic SIV-infected macaques had elevated levels of immune activation and inflammation in adipose tissue together with an increase in adipocyte density and reduced adipocyte size compared to uninfected controls. While previous studies have implicated antiretroviral drugs as a major driver of adipose dysfunction, these findings point to a possible direct effect of SIV infection per se on adipogenesis. Alterations in adipogenesis could impair metabolic functions and potentially augment their proinflammatory properties during HIV/SIV infection [5]. Interestingly, immunophenotyping of the adipose SVF revealed a decrease in CD4⁺ T cells and a concomitant increase in both frequency and absolute numbers of CD8⁺ T cells in both SCAT and VAT compartments. Using immunohistochemistry, CD8⁺ T cells were found near the capillary area, while central memory CD4⁺ T cells were located close to the adipocytes suggesting that unlike CD8⁺, CD4⁺ T cells were not recent migrants from peripheral blood. Although unaddressed, these findings raise interesting questions regarding the location and trafficking of immune cells within adipose tissue including the existence of a cross talk between adipocytes and CD4⁺ T cells in the maintenance of latent reservoirs. Analysis of T cell maturation subsets showed a predominance of central memory CD4⁺ T cells and effector memory CD8⁺ T cells in both SCAT and VAT. In addition, both populations exhibited a higher activation state than peripheral blood cells based on HLA-DR and CD69 expression. The presence of larger numbers of central memory CD4⁺ T cells in both SCAT and VAT is an important finding as these long-lived memory cells with homeostatic proliferation capacity can ensure prompt replenishment of the latent HIV reservoir pool. It would be intriguing to know whether these cells remain trapped within adipose tissue or are capable of re-entering the circulation. Further, adipose resident macrophages (CD45⁺CD3⁻CD14⁺) were found to be highly activated and displayed an inflammatory phenotype (CD206⁻/CD163⁻). The latter findings are important, as macrophages have been implicated in the maintenance of a persistent low-grade chronic inflammation in obese individuals [6]. This persistent pro-inflammatory milieu may alter both immune and metabolic homeostasis thereby promoting insulin resistance and increasing the risk of type 2 diabetes, cardiovascular disease, and other HIV related co-morbidities. Furthermore, the identification of SIV DNA and RNA by quantitative reverse transcription polymerase chain reaction and *in situ* hybridization, respectively, in total SVF cells and sorted CD4⁺ T-cells and CD14⁺ macrophages provided strong evidence of viral production in adipose tissue.

Finally, using surgically collected adipose samples from ART-treated patients the authors successfully detected both HIV DNA and RNA in SVF of all samples, thus confirming the presence of replication competent virus in this compartment [3]. Replication competent HIV was also detected in sorted *ex vivo* activated adipose derived CD4⁺ T cells from six aviremic ART-treated patients. An earlier study by Courtier *et al.* published in *AIDS* also identified adipose tissue as a HIV reservoir using SVF cells [7]. Although, Courtier *et al.* found CD4⁺ T cells in SVF to be highly activated memory cells harboring integrated HIV DNA, the individual contribution of CD4⁺ T cells and macrophages to maintenance of the HIV reservoir could not be established as total SVF cells were used for HIV DNA measurement.

Overall, these studies indicate that adipose tissue can serve as a sanctuary site containing replication competent HIV in ART-treated individuals. In addition, adipose tissue redistribution following HIV infection and/ART treatment could play a major role in causing persistent inflammation and immune activation with direct relevance to both HIV related co-morbidities and disease progression.

It is worth pointing out that in obesity the adipose tissue undergoes dynamic immunological changes to a pro-inflammatory state characterized by an influx of immune cells (primarily CD8⁺ T lymphocytes and macrophages) that secrete high levels of pro-inflammatory cytokines (TNF- α and >35% of circulating IL-6) [8–9]. Given the similarities with HIV/SIV infection, anti-inflammatory strategies to reduce CD8⁺ T cell and macrophage infiltration, promote M2 macrophage polarization, increase T_{REG} and myeloid derived suppressor cell numbers, and to restore adipocyte homeostasis should be explored in HIV/SIV infection. Future studies could also focus on addressing the sequence of events and mechanisms that lead to activation of these diverse immune cell populations and adipocytes during HIV/SIV infection. For HIV/SIV researchers, advancements in the obesity literature can foster cross-fertilization of research ideas that could stimulate new directions for research or development of novel strategies to reduce adipose dysfunction/inflammation and AIDS related co-morbidities. Further studies are needed to precisely delineate the effect of HIV/SIV and ART on adipogenesis and its relationship with persistent inflammation and the pathogenesis of co-morbidities. The question of optimal antiretroviral drug penetration in adipose tissue and their impact on HIV reservoir size and persistence merits future investigation. Lastly, these studies emphasize the need to develop broader approaches to identify and characterize the size and magnitude of other potential viral niches, particularly in the setting of virally suppressive ART so that novel strategies to induce HIV remission can be explored for a possible HIV cure.

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