Commentary

How integral is the α4β7 integrin to HIV transmission?

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ARTICLE INFO

Article History:
Received 11 November 2020
Accepted 13 November 2020

Defining the α4β7 integrin from an immunologic perspective is relatively straightforward. This heterodimeric glycoprotein is found on activated CD4+ T cells that also express high levels of CCR5, and after binding to its natural ligand (mucosal addressin cell adhesion molecule-1, or MAdCAM-1) it acts as a homing receptor that mediates lymphocyte migration to gut-associated lymphoid tissue (GALT) [1]. Studies from almost twenty years ago found that expression of this gut-homing integrin on T cells was specifically induced after antigen presentation by dendritic cells derived from Peyer’s patches in the gut, but not by those derived from the spleen or lymph nodes [2], demonstrating an immune mechanism to “home” responsive T cells back to the mucosal site of pathogen challenge. However, defining the role of α4β7 in HIV susceptibility and pathogenesis has proved to be much more challenging, and the elegant study from Martin and colleagues in EBioMedicine reveals that α4β7 might not have as clear-cut a role in transmission as was previously thought.

SIV/HIV infection causes severe depletion of CD4+ T cells from the gut mucosa in the earliest stages of HIV infection, regardless whether the virus was acquired across the gut mucosa, the genital mucosa or parenterally [4]. Given the high expression of α4β7 on gut T cells, this led Arthos and colleagues to first study its role in cellular HIV susceptibility, with the finding that α4β7 expression enhances HIV susceptibility and replication at a cellular level, and that early transmitted viruses demonstrate enhanced binding to this integrin [reviewed in [5]]. Subsequently some groups have confirmed these findings while others have not [6], and there are also conflicting findings regarding the role of α4β7 in HIV pathogenesis and virus reservoir formation, a topic that is beyond the scope of this commentary but nicely reviewed elsewhere [6].

Given the controversy regarding the impact of α4β7 on HIV susceptibility at the level of the individual cell, investigators then assessed whether the frequency of α4β7 expression at the host level is associated with global differences in SIV/HIV susceptibility. Martineilli and colleagues demonstrated in macaques that the frequency of α4β7high CD4+ T cells in the blood correlated closely with that in colorectal tissues, and also predicted primate susceptibility to a rectal SIV challenge [7]. Human studies confirmed that α4β7 expression on CD4+ T cells from the blood and gut are linked [8], that the proportion of α4β7high CD4+ T cells in blood is relatively stable over time [9], and that conditions that enhance host HIV susceptibility such as Herpes simplex virus type 2 (HSV-2) infection are associated with increased α4β7 expression on blood CD4+ T cells [10]. Most relevant to the Martin study, Sivro and colleagues compared α4β7 expression on blood CD4+ T cells between South African women who acquired HIV and matched controls who remained HIV uninfected; samples were collected a median of 110 days before HIV infection, and the frequency of β7high CD4+ T cells (a surrogate for α4β7 expression) in blood correlated with subsequent sexual HIV acquisition, as well as with the rate of post-infection CD4+ cell decline [8].

In order to extend these findings from heterosexual women into other HIV-at-risk populations, Martin and colleagues [3] now explore whether α4β7 expression on blood CD4+ T cells is also associated with HIV acquisition risk among men who have sex with men (MSM) and/or people who inject drugs (PWID). These questions were addressed in two very well-described cohorts, namely the HVTN 505 vaccine trial (MSM) and the ALIVE cohort (PWID). In the first instance, cryopreserved peripheral blood mononuclear cells (PBMC) were compared between MSM who acquired HIV during the HVTN 505 vaccine trial (N=103) and matched controls (N=103), using samples collected within the year preceding HIV acquisition. Interestingly, no correlation or trend was apparent between β7high CD4+ T cell expression and HIV acquisition, either in unadjusted or adjusted analysis. A similar approach was used to assess the impact of α4β7 expression on HIV acquisition among PWID participants from the ALIVE cohort, using PBMC collected a median of 1.4 years prior to HIV acquisition. In this cohort, cases acquiring HIV (N=49) actually demonstrated a significantly lower frequency of α4β7 expression on blood CD4+ T cells than controls (N=143) in unadjusted analysis, and this inverse association was even stronger after adjusting for age, sex, ethnicity, injection drug use in the past six months, and number of sexual partners. Furthermore, no association was seen among PWID between pre-acquisition α4β7 expression and rates of CD4+ T cell decline after HIV infection.

The lack of an association between α4β7 expression and HIV acquisition among MSM is unexpected, given that this integrin home activated T cells to the gut mucosa and that most acquisition
among MSM occurs across the rectal mucosa. While the lack of association with acquisition in PWID is perhaps less surprising, given the parenteral route of virus transmission, one would certainly not have expected to find HIV acquisition to be associated with lower α4β7 expression. Furthermore, it is also unclear why blood expression levels of α4β7 would predict HIV disease progression in heterosexual women, but not in PWID. Sample size is unlikely to be the issue, as each cohort size in the Martin study [3] exceeds that in the Sivro study from South Africa [8]. Appropriate statistical adjustment was made for potential confounders where possible, although data were not available for some parameters linked to both HIV risk and α4β7 expression, such as HSV-2 serostatus. While the authors suggest that the relationship between α4β7 and HIV acquisition might only apply to heterosexual transmission, it is not intuitively obvious why this would be the case. Therefore, while the Martin study is carefully performed and certainly a welcome addition to the literature, whether α4β7 expression increases HIV risk — and hence whether α4β7 would be an attractive target for clinical strategies such as pre-exposure prophylaxis (PrEP) — remains an unresolved question.

Declaration of Competing Interest

The authors declare no competing interests.

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