HHS Public Access

Author manuscript

Trends Immunol. Author manuscript; available in PMC 2018 August 14.

Published in final edited form as:

Trends Immunol. 2017 July ; 38(7): 457–458. doi:10.1016/j.it.2017.04.007.

Signature of the Sleeper Cell: A Biomarker of HIV Latency Revealed

Satish K. Pillai[1,*] and **Steven G. Deeks**[2]

[1]Blood Systems Research Institute and Department of Laboratory Medicine, University of California, San Francisco

[2]Positive Health Program, University of California, San Francisco

Abstract

HIV establishes a reservoir in latently infected T cells, and this reservoir has long hampered curative approaches. A recent study by Descours et al. identifies CD32a as a marker of latently infected T cells, potentially opening the way to the development of strategies that directly target this critical HIV reservoir.

Two decades have passed since the seminal discovery that HIV establishes latent infection in long-lived memory CD4+ cells *in vivo*, undermining the capacity of antiretroviral therapy to achieve a sterilizing cure (1, 2). Further complicating this daunting reality, HIV latently-infected cells have done an exemplary job of blending into the woodwork, remaining invisible to the host immune system and to scrutinizing scientists alike. Despite countless efforts to identify a marker of latent cells (often described as the “Holy Grail” of the HIV cure world), a satisfyingly sensitive and specific signature of these cells has remained infuriatingly elusive. This curse, however, may finally be broken. Reporting in the journal *Nature*, Descours and colleagues have recently revealed that the low-affinity receptor for the immunoglobulin G Fc fragment, CD32a, may prove to be a reliable albeit incomplete cell-surface signature of CD4+ T cells harboring latent HIV genomes (3).

While earlier biomarker discovery efforts were mainly inspired by knowledge of how HIV reshapes the immune system (with much attention focused on a spectrum of “activation” markers) (4), the Montpellier-based team led by Benkirane employed a non-hypothesis-driven, sequential *in vitro* and *in vivo* approach to identify potential biomarkers of the latent reservoir in CD4+ T cells. First, the group implemented their previously developed HIV latency model (5), infecting quiescent primary CD4+ T cells with an engineered viral reporter construct that enables differentiation of infected and uninfected cells. These cells were then subjected to comprehensive transcriptomic profiling and confirmatory protein work, to identify cell-surface markers that were specifically and potently upregulated in latently-infected cells. Several hits were obtained, with the most promising being CD32a. Then, the group transitioned into critical translational experiments to validate CD32a as a

*Corresponding author: Satish K. Pillai, Ph.D., Blood Systems Research Institute, 270 Masonic Avenue, San Francisco, CA 94118, satish.pillai@ucsf.edu, Tel: (415) 513-4461, Fax: (415) 567-5899.

Conflicts of Interest: The authors report no conflicts of interest.

biomarker of the latent reservoir *in vivo*. Using sophisticated molecular and virologic techniques, they determined that CD32a+ CD4+ T cells obtained from the blood of HIV-infected, treatment-suppressed individuals were enriched over 1,000-fold for the presence of replication-competent HIV (as compared to CD32a- CD4+ T cells). As the vast majority of HIV genomes are genetically defective (6), these data provide key evidence that CD32a+ cells harbor a legitimate viral reservoir that is capable of recrudescence, and do not simply represent an irrelevant graveyard of dead-end viral genomes.

If confirmed, these findings represent a real advance in our efforts to identify a cure for HIV disease. A true cure would require complete elimination of virus in an infected individual. Such an outcome will most likely be achieved by targeting and then eradicating the cellular reservoir of HIV, eliminating the possibility that the virus will re-emerge when antiretroviral therapy is stopped. With the notable exception of the Berlin Patient, who received an allogeneic stem cell transplantation for another disease from an individual homozygous for a CCR5 mutation conferring resistance to HIV (7), our eradication attempts thus far have only had modest outcomes. Our lack of progress is due in large part to our limited comprehension and definition of the latently-infected cell as it exists in nature. The CD32a story advances our capacity to precisely identify the reservoir by a few orders of magnitude. Understanding the biology that explains why CD32a is such a specific marker will almost certainly advance our knowledge even further.

Curative approaches have generally been crude and non-specific. For instance, the pharmacologic agents used to implement the “shock-and-kill” cure strategy (8), involving reactivation of latent virus, have no in-built specificity; infected and uninfected cells are indiscriminately targeted in such interventions. The discovery of CD32a as the billboard atop latent cells radically changes the ball game. In theory, we now have information in hand that will enable us to target and eliminate latently infected cells with surgical precision, using anything from designer nanoparticles to aptamers to garden-variety antibodies. Beyond serving as a convenient and welcome bullseye for infected cells, the CD32a molecule may even constitute a key component of the death knell itself; the biological activity of CD32a and its known functions in antigen uptake and immune signaling (9) may be incorporated into the modus operandi of the eradication approach.

On a slightly more mundane note, the identification of CD32a will likely have a significant impact on the development of cure-focused HIV diagnostics in the near-term. The field has been sorely lacking for clinical indicators that enable convenient evaluation of curative interventions. Extrapolating from the observations reported, it may be possible to gauge erosion of the latent reservoir in response to a cure drug by simply tracking shifts in the frequency of CD32a+ T cells.

Despite the surge of enthusiasm that the CD32a revelation has brought to the field, it is early days yet, and a finding of this magnitude must be handled with caution and care. As a key first step, the generalizability of this relationship between CD32a expression and HIV persistence needs to be established by investigative teams with complementary capacities. In particular, it has become increasingly evident that the HIV reservoir largely resides in lymphoid tissues and that the tissue-resident cells which harbor the virus are distinct from

those that circulate. For example, CD4+ T follicular helper cells that reside in B cell follicles are now widely believed to be a major reservoir for the virus (10), particularly during untreated and early-treated disease. Until proven otherwise, the biology of these cells should be assumed to be distinct from circulating CD32a-expressing cells. As the reported data only describe expression in blood cells, extensive and challenging tissue work will be needed to demonstrate that the prognostic significance of CD32a translates beyond the vasculature to the tissue microenvironment.

Moving past questions of anatomic niche, there are many questions of the “Why?” and “How?” nature surrounding the CD32a story that will need addressing to fully exploit the biomarker. It is entirely unclear how establishment of latent HIV infection in the CD4+ T cell compartment results in the peculiar and serendipitous induction of CD32a expression on the surface of a cell that generally does not express this receptor (CD32a is typically present on myeloid rather than lymphoid cells). Furthermore, it is not obvious at this stage if CD32a + cells are particularly susceptible to becoming infected, if CD32a is part of the cellular response to infection, or if CD32a induction is directly triggered by the always surprising virus as part of its life cycle. The latter may represent a strategy to increase the likelihood that the cell (and virus within) are reactivated, or may constitute a program to reinforce the latent state and long-term survivorship (evolutionary hypotheses based on individual and group selection, respectively).

There are also known biological aspects of CD32a that will complicate its utility in the near-term. Although CD32a may only ever pop up on latently infected CD4+ T lymphocytes, the literature reports that CD32a is constitutively expressed on several other cell types, including monocytes and platelets (9). Therefore, it is unlikely that this marker could be targeted in isolation by a pharmaceutical smart bomb; the juxtaposition of CD32a with other markers (e.g. lineage markers including CD3 and CD4) will have to be exploited by targeted delivery approaches to maintain specificity. These technicalities and ponderings aside, the discovery of CD32a as a biomarker of the latent HIV reservoir will certainly stimulate a cornucopia of ideas and inquiries in the immediate future.

Acknowledgments

Funding: S.K.P. is supported by R01GM117901 and R01MH112457 from the National Institutes of Health, and amfAR 109111-57-RGRL; S.K.P and S.G.D. are supported by the amfAR Institute for HIV Cure Research.

References

1. Wong JK, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. Science. Nov 14.1997 278:1291. [PubMed: 9360926]
2. Finzi D, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science. Nov 14.1997 278:1295. [PubMed: 9360927]
3. Descours B, et al. CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses. Nature. Mar 23.2017 543:564. [PubMed: 28297712]
4. Fromentin R, et al. CD4+ T Cells Expressing PD-1, TIGIT and LAG-3 Contribute to HIV Persistence during ART. PLoS Pathog. Jul.2016 12:e1005761. [PubMed: 27415008]
5. Descours B, et al. SAMHD1 restricts HIV-1 reverse transcription in quiescent CD4(+) T-cells. Retrovirology. Oct 23.2012 9(87)

6. Ho YC, et al. Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. Cell. Oct 24.2013 155:540. [PubMed: 24243014]
7. Hutter G, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med. Feb 12.2009 360:692. [PubMed: 19213682]
8. Deeks SG. HIV: Shock and kill. Nature. Jul 25.2012 487:439. [PubMed: 22836995]
9. Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. Nat Rev Immunol. Jan.2008 8:34. [PubMed: 18064051]
10. Perreau M, et al. Follicular helper T cells serve as the major CD4 T cell compartment for HIV-1 infection, replication, and production. J Exp Med. Jan 14.2013 210:143. [PubMed: 23254284]