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Commentary

Discontinued antiretroviral therapy (ART) results in uncontrolled HIV replication in most cases. How the virus population that persists during ART escapes immune control remains unknown. In this issue of the *JCI,* Mitchell and authors investigated plasmacytoid dendritic cells (pDCs) from the blood of individuals living with HIV. After ART was discontinued and as the virus began to spread, an apparently functional pDC response emerged. Notably, these pDCs were initially capable of producing high levels of type I IFN, but rapidly lost this capacity, even before the virus became readily detectable in blood. This study suggests that dysfunctional pDCs are a key initial mechanism associated with poor HIV control. These innate immune responses might be targeted in the emerging efforts to cure HIV disease.

The immune response fails to control HIV early in initial virus spread

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Discontinued antiretroviral therapy (ART) results in uncontrolled HIV replication in most cases. How the virus population that persists during ART escapes immune control remains unknown. In this issue of the *JCI*, Mitchell and authors investigated plasmacytoid dendritic cells (pDCs) from the blood of individuals living with HIV. After ART was discontinued and as the virus began to spread, an apparently functional pDC response emerged. Notably, these pDCs were initially capable of producing high levels of type I IFN, but rapidly lost this capacity, even before the virus became readily detectable in blood. This study suggests that dysfunctional pDCs are a key initial mechanism associated with poor HIV control. These innate immune responses might be targeted in the emerging efforts to cure HIV disease.

Host response to HIV recrudescence

Although antiretroviral therapy (ART) is able to suppress HIV replication, it is not curative. HIV persists during ART in a latent reservoir composed of memory $CD4^+$ T cells and perhaps monocytes and macrophages. When ART is interrupted, high-level virus replication typically ensues, with a two- to four-week delay between the interruption and the time of detectable viremia. Once the virus begins to successfully replicate, it expands exponentially, resulting in massive $CD4^+$ T cell depletion and, in most individuals, an overwhelmed immune system that can never catch up. The precise mechanism by which the recrudescing virus population escapes immune control after ART is unknown. There are also no viable biomarkers that predict when the virus will rebound, or who might be one of the rare individuals whose post-ART viremia remains controlled (post-treatment controllers).

In this issue of the *JCI*, Mitchell and colleagues provide unique and provocative data on the earliest virus-host interactions during the post-ART period (1). The authors used a well-characterized cohort of adults living in Thailand who started ART during acute/early infection and who subsequently underwent a planned analytical treatment interruption (ATI). A total of 29 individuals (all but one of whom were male) were studied. Many were enrolled in clinical trials of various cure interventions, although 16 interrupted ART in the absence of any other treatment. Samples were available prior to interruption, after ART but prior to the emergence of detectable viremia, and after rebound.

As a first step toward understanding the host response to HIV recrudescence, Mitchell and colleagues (1) focused on plasmacytoid dendritic cells (pDCs). These cells are among the earliest first-responders during acute viral infections. Viral nucleic acid binds TLRs and induces a rapid and robust production of type I IFNs; these cytokines in turn have a complex and pleiotropic effect on all components of the immune system, particularly T cells, which are widely assumed to be primary mediators of HIV control (2). In nonhuman primates acutely infected with SIV, the inhibition of these pathways results in rapid disease progression and death (3), illustrating the key role that IFN plays during acute viral infections.

In the Thai cohort, Mitchell and colleagues found that soon after interrupting ART — but, importantly, prior to detectable systemic viremia — the frequency and activation state of circulating blood pDCs increased, as might be expected (1). These cells initially showed the capacity to release high levels of IFN. However, within one week in most cases, circulating pDCs notably downregulated IFNα production after in vitro challenge (Figure 1A and ref. 1). This loss of function occurred prior to rebound in viremia, leading the authors to speculate that pDC dysfunction plays a role in loss of virus control. Moreover, prior to detectable viremia, pDCs showed lower expression of integrin β7, a cell membrane–bound trafficking molecule, suggesting that these cells were unable to migrate to mucosal sites where the virus largely resides and replicates (4).

Predicting viremia rebound

In addition to providing potential mechanistic insights, these data (1) suggest that careful monitoring of the host response during a treatment interruption might lead to the discovery of a biomarker that could predict a pending rebound in viremia. Currently, there are no well-validated methods to measure the total body size of the replication-competent reservoir. There are also no validated assays to determine whether a therapeutic intervention has induced an effective anti-HIV response. Accordingly, the most reliable way to determine the effectiveness of a curative strategy is to interrupt therapy and carefully monitor viral load. Such treatment interruptions are risky, as the acute viremia can cause morbidity and greatly increase the likelihood that the virus will be transmitted sexually (5). A method to monitor early virus activity during a treatment interruption is hence

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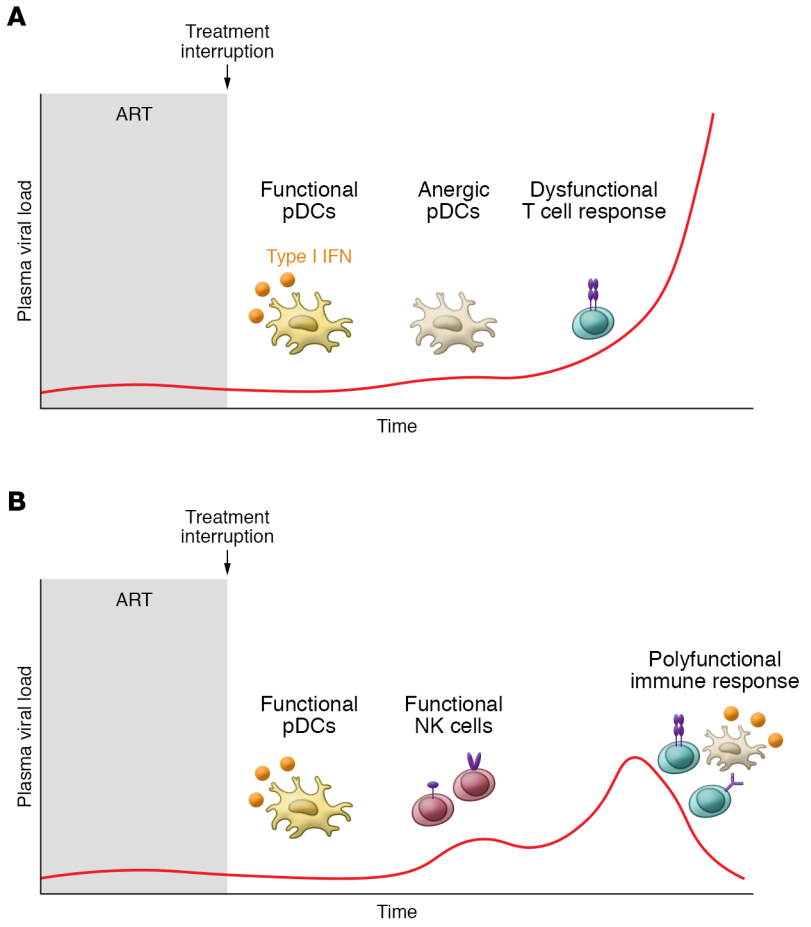

Figure 1. Immune response following ART interruption. (**A**) In the majority of individuals, ART cessation results in an initial immune response that involves activation of pDCs and production of IFN. Mitchell and colleagues found that this initial immune response was followed by a period of anergy within the pDC compartment, which, they hypothesized, leads to a dysfunctional immune response and subsequent loss of viral control. (**B**) In contrast to the typical noncontrollers who rebound after ART, some individuals exhibit durable control (post-treatment controllers), which presumably occurs by generating and maintaining a polyfunctional, robust immune response.

urgently needed. A marker related to the host response (e.g., pDC numbers or IFN levels) may provide early evidence that systemic spread is imminent. Notably, CD30 expression on T cells increases just prior to virus recrudescence (6, 7); the mechanism for this observation is unknown, but, notably, CD30 is also involved in the innate immune response, as it is a member of the TNF receptor family.

Conclusions and future directions

Although the work of Mitchell and colleagues (1) is innovative and sure to be impactful, the study has limitations, as noted by the authors. First and foremost, many of the individuals studied received broadly neutralizing HIV-specific antibodies during the interruption (these antibodies have potent effects on both the virus and host response; ref. 8). Only 16 of the 29 participants interrupted therapy without any other interventions (all of the trends in these individuals were consistent with those in the larger cohort). Second, these studies were not designed to fully explore how the virus and host interact during the pre-rebound stage. To address this question, prospective studies in which blood and tissues samples are collected more frequently are needed; such studies are technically challenging but possible (9, 10). Third, the vast majority of individuals exhibited rapid rebound soon after ART was interrupted, making it difficult to characterize longitudinally how the immune response eventually failed.

Notably, we previously reported a unique case of an individual who started ART very early and had no measurable reservoir (6). During a planned test-of-cure interruption protocol, blood was sampled weekly. The virus eventually rebounded 225 days after therapy was interrupted. Trace levels of virus activity were observed several weeks before the rebound; during this time, the frequency of cells expressing CD30 increased. Similar observations were subsequently made in a retrospective analysis of multiple treatment interruptions (7). Once a larger number of cases such as this one are identified, or preferably, once effective curative interventions are developed, deep longitudinal studies to compare those who reach prolonged virus-free remission with those who fail to control the virus may be possible (Figure 1B).

Perhaps the most important conceptual advance in this study is that careful interrogation of the immune system just as HIV begins to spread after ART can provide unique information regarding why the immune system typically fails to control HIV. The pDC activation observed by Mitchell and colleagues (1) and the CD30 story are likely just the beginning. To more comprehensively address these questions, highly monitored treatment interruption protocols, in which extensive blood and tissue sampling occurs before rebound, are needed. An unbiased approach to characterize the immune response, as well as changes in the microbiome, virome, and proteome will almost certainly be very informative. Inspired by this study, we and others are planning such clinical studies.

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1. Mitchell JL, et al. Plasmacytoid dendritic cells sense HIV replication before detectable viremia following treatment interruption. *J Clin Invest*. 2020;130(6):2845–2858.
2. O'Brien M, Manches O, Bhardwaj N. Plasmacytoid dendritic cells in HIV infection. *Adv Exp Med Biol*. 2013;762:71–107.
3. Sandler NG, et al. Type I interferon responses in rhesus macaques prevent SIV infection and slow disease progression. *Nature*. 2014;511(7511):601–605.
4. Estes JD, et al. Defining total-body AIDS-virus burden with implications for curative strategies. *Nat Med*. 2017;23(11):1271–1276.
5. Julg B, et al. Recommendations for analytical antiretroviral treatment interruptions in HIV research trials-report of a consensus meeting. *Lancet HIV*. 2019;6(4):e259–e268.
6. Henrich TJ, et al. HIV-1 persistence following extremely early initiation of antiretroviral therapy (ART) during acute HIV-1 infection: an observational study. *PLoS Med*. 2017;14(11):e1002417.
7. Prator CA, et al. Circulating $CD30^+CD4^+$ T cells increase before human immunodeficiency virus rebound after analytical antiretroviral treatment interruption. *J Infect Dis*. 2020;221(7):1146–1155.
8. Niessl J, et al. Combination anti-HIV-1 antibody therapy is associated with increased virus-specific T cell immunity. *Nat Med*. 2020;26(2):222–227.
9. Rothenberger MK, et al. Large number of rebounding/founder HIV variants emerge from multifocal infection in lymphatic tissues after treatment interruption. *Proc Natl Acad Sci USA*. 2015;112(10):E1126–E1134.
10. De Scheerder MA, et al. HIV rebound is predominantly fueled by genetically identical viral expansions from diverse reservoirs. *Cell Host Microbe*. 2019;26(3):347–358.e7.