Twenty years of HIV-1 research: what the future holds

This year marks the 20th anniversary of the discovery of HIV-1, the causative agent of AIDS. In 2003, 16,000 people are still becoming infected with HIV every day, and many of them do not have access to antiretroviral drug therapy. Attempts during the last two decades to develop a vaccine against HIV-1 have failed in inducing sterilizing immunity (blocking virus entry) or protection from AIDS (delaying disease progression). This is largely a consequence of the virus' variability and inability to induce adequate T cell–mediated immunity, in the context of stubborn elusiveness to virus neutralization by antibody.

The mechanisms responsible for the favorable outcome in long-term nonprogressors (LTNPs) and exposed individuals who do not become infected are ascribed to both the host immune system and the virus. Accumulating evidence suggests that maintenance of strong and fully functional HIV-1–specific $CD4^+$ and $CD8^+$ T cell responses in LTNPs is essential for the control of viremia, resulting in clinical benefits, prolonged survival and reduced viral replication[1,2].

Unlike LTNPs, most infected individuals show dysfunctional HIV-1–specific T lymphocyte responses early during infection, before the decline in $CD4^+$ T cell numbers. The introduction of effective antiretroviral combinations in 1995 revolutionized treatment of HIV-1 infection by allowing substantial control over viral replication. However, despite increasing the numbers of $CD4^+$ T cells, potent antiretroviral therapy (ART) is unable to reverse the progressive, variable decline of HIV-1-specific $CD4^+$ and $CD8^+$ T cell responses during the course of HIV-1 infection.

Activation, release of soluble mediators and proliferation of $CD4^+$ helper T lymphocytes (HTLs) are required for an appropriate antiviral response to be mounted. The relationship between HTLs and cytotoxic T lymphocytes (CTLs) is mediated by fully functional ('helped', and therefore activated) antigen-presenting cells (APCs) such as dendritic cells (DCs) and/or macrophages[3].

$CD4^+$ HTLs are targets of HIV-1, even in the early phases of infection[4]. In 1998, the discovery of latent viral reservoirs during ART dampened hopes for virus eradication. The major HIV-1 reservoir is resting memory $CD4^+$ HTLs bearing integrated HIV-1 DNA[5]. Virus captured on follicular DCs within lymphoid tissues also presents a continuous, nonexhaustive source of viral antigen. As productively infected DCs and macrophages have also been observed, defects in overall cellular immune responses could be attributed to infection of such fundamental immune components. In addition, infection of other types of cells, such as thymic epithelial cells, may destroy the thymic microenvironment and irrevocably interfere with T cell developmental pathways[6].

In considering immunological changes, it is difficult to draw a line between cause and effect. T cell dysfunction may be induced by several mechanisms of peripheral unresponsiveness. The relative contributions of destruction, redistribution and/or decreased production to $CD4^+$ HTL dysfunction during infection remain under contention. Although both *in vivo* and *in vitro* nonspecific responses improve upon initiation of ART, the inability to restore HIV-1-specific T cell responses may result from the continuation of HIV-1-induced unresponsiveness and dysfunction. Nevertheless, it is encouraging that even in late-stage HIV-1 disease, suppression of HIV-1 replication combined with immunomodulation can induce recovery of both $CD4^+$ and $CD8^+$ HIV-1–specific T lymphocytes[7].

When considering virus variability, future HIV-1 research must focus on responses elicited by prophylactic immunization and those requiring improvement by post-infection immunotherapy. Induction of HIV-1–specific immune responses in seronegative vaccine recipients at the level seen in exposed but uninfected individuals, and induction of such responses in HIV^+ individuals at the levels seen in LTNPs, will be achieved with potent prophylactic vaccines or with ART plus or minus immunotherapy, respectively. The success of immunotherapy will very much depend on the preservation of the microenvironments where T cell development and activation occur. The fact that after ART the virus persists in the very sites associated with T lymphocyte selection and activation events implies that HIV-1 may continue to interfere with these events. Dissecting out differences in the gene expression profiles of functional and dysfunctional HIV-1-specific T cells may illuminate approaches for prophylactic and therapeutic interventions.

Understanding how HIV-1–specific $CD4^+$ HTLs provide help for effector and memory virus-specific CTLs, and why HIV-1–specific $CD4^+$ HTL responses disappear or do not fully develop in most infected individuals, will yield clues to successful vaccine design and future immunotherapeutic approaches. This, in turn, may lead to the elusive sterilizing immunity sought for the last 20 years. Review and careful evaluation of the methodology available for quantification of HIV-1-specific responses and of the relationship between observed *in vitro* responses and those known to occur *in vivo* remain paramount.

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