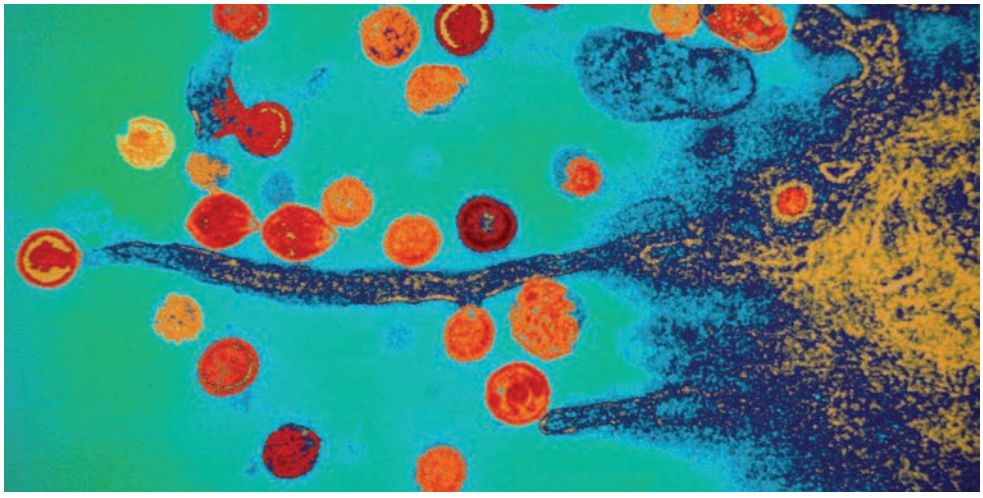
MILESTONE 12

CD8s crave control



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Understanding how the human immune system responds to HIV-1 infection is critical to inform the development of protective vaccines. In 1987, Bruce Walker and colleagues reported that HIV-1-infected individuals had circulating T cells that recognized and killed target cells expressing HIV-1 proteins in vitro. But whether cytotoxic T lymphocytes (CTLs) could thereby control virus levels in humans was initially unclear.

To address the influence of CTLs on the virus—and vice versa—Rodney Phillips and colleagues analyzed the longitudinal responses of CTLs specific for the HIV-1 Gag protein in three HIV-infected individuals. The researchers showed fluctuations over time in terms of the specific epitopes recognized and the dominance of CTL specificities. They further found mutations arising in or near T cell epitopes in Gag and the failure of some CTLs to recognize altered epitopes. Their results suggested that amino acid variation in viral epitopes abolishes recognition by CTLs, which may confer a survival advantage to the virus by enabling immune escape.

So, could viral control be achieved by CTLs in HIV-1 infection? In 1994, two studies in humans and a further study in monkeys suggested that $CD8^+$ T cells do not simply play a bystander role in HIV infection, but instead are temporally linked to the control of viremia during the acute phase of infection.

Analyzing five early-stage HIV-1-infected individuals, Richard Koup and colleagues found $CD8^+$ T cell responses to HIV-1 Gag, Pol and Env proteins, including at time points when no neutralizing antibody response to autologous virus was yet detectable. Four of the five patients had measurable CTL responses at early time points after symptom presentation, while the one patient lacking this early response failed to control virus levels.

In a separate group of five patients, Persephone Borrow and colleagues showed that individuals who cleared infectious virus from the plasma within the first few weeks of symptom onset, and maintained virus control for more than a year, had strong $CD8^+$ T cell responses to HIV-1 gp160, Gag and Tat proteins. Patients lacking a strong HIV-1-specific CTL response had reduced ability to clear the virus and sustain control of virus levels. All of the patients lacked HIV-1-specific antibodies at the time of symptom presentation, although they later seroconverted. However, the timing of induction of antibodies after observable $CD8^+$ T cell responses suggested, in both studies, that CTLs are the initial responding cells that exert control over the virus during early infection.

Extending these findings, Jörn Schmitz and colleagues provided causal evidence in rhesus macaques that $CD8^+$ T cells restrict SIV infection. Following virus inoculation in monkeys (and similarly to the trajectory of HIV-1 infection in humans), levels of SIV peak and then rapidly decline by 21 days after infection. When researchers depleted $CD8^+$ T cells during primary acute SIV infection, the animals failed to show this rapid decline in virus levels. In one animal with transient depletion of $CD8^+$ T cells, recovery of SIV-specific CTL responses was coincident with restored control of virus in blood, while in one animal that failed to regain $CD8^+$ T cells viremia was never controlled. The findings provided definitive evidence that $CD8^+$ T cells constrain viremia in the SIV model of HIV infection.

> “$CD8^+$ T cells constrain viremia”

Genetic evidence supporting the critical importance of $CD8^+$ T cells in modulating HIV disease came from a genome-wide association study of HIV-1 controllers—HIV-1-infected individuals who control viral replication long term in the absence of antiretroviral therapy—and HIV-1 progressors. The only single-nucleotide polymorphisms of genome-wide significance that associated with HIV-1 control mapped to the major histocompatibility complex genes, and specifically to a region focused around the class I human leukocyte antigen genes, which restrict $CD8^+$ T cell responses. Collectively, these and other studies demonstrate the crucial role of $CD8^+$ T cells in controlling the outcome of HIV-1 infection—by exerting epitope-targeted immune pressure, CTLs can both constrain HIV-1 and force its evolution, causing loss of viral fitness or enabling viral outgrowth and disease progression.

Alison Farrell, *Nature Medicine*

ORIGINAL ARTICLES Phillips, R. E. et al. Human immunodeficiency virus genetic variation that can escape cytotoxic T cell recognition. *Nature* **354**, 453–459 (1991) | Koup, R. A. et al. Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. *J. Virol.* **68**, 4650–4655 (1994) | Borrow, P., Lewicki, H., Hahn, B. H., Shaw, G. M. & Oldstone, M. B. Virus-specific $CD8^+$ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. *J. Virol.* **68**, 6103–6110 (1994) | Schmitz, J. E. et al. Control of viremia in simian immunodeficiency virus infection by $CD8^+$ lymphocytes. *Science* **283**, 857–860 (1999)

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