MILESTONE 10

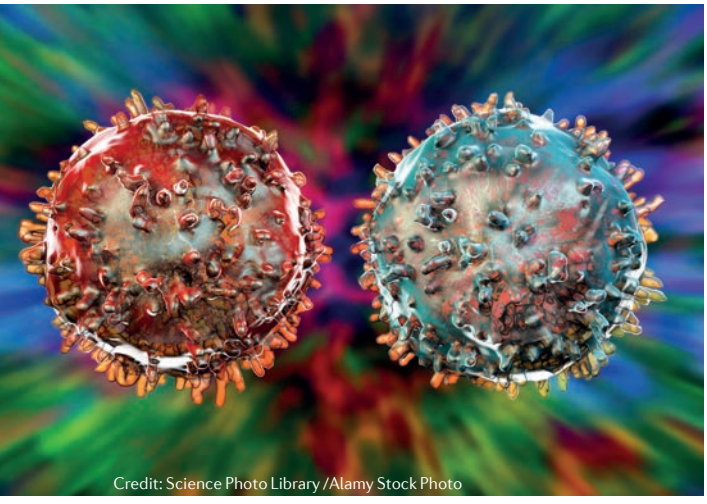
Immune activation linked to pathogenesis

After the description of CD4 as a receptor for HIV-1 (MILESTONE 3), it was generally assumed that infection of $CD4^+$ T cells by HIV-1 would drive loss of these cells and subsequent development of AIDS. However, it gradually became apparent that chronic immune activation, rather than immunodeficiency alone, was a feature of progressive HIV-1 disease.

The very first description of AIDS (MILESTONE 1) had reported increased levels of the surface activation marker T10 (later called CD38) on T cells from the peripheral blood of patients. Other studies in the early 1980s by scientists such as Janis Giorgi, John Fahey and Anthony Fauci showed that HIV-1 infection is associated with the upregulation of activation markers on $CD8^+$ T cells and B cells.

An important insight came in 1990, when a study by Fahey, Giorgi and co-workers showed that increased expression of immune activation markers was linked to disease progression in patients with HIV-1. They found that higher serum levels of neopterin (a metabolite of interferon-γ-activated macrophages) and the major histocompatibility complex (MHC) class I component β2-microglobulin were almost as powerful as $CD4^+$ T cell counts in predicting AIDS progression in HIV-1-infected patients. A later study from the laboratory of Giorgi reported that higher expression of CD38 on $CD8^+$ T cells was a better predictive marker for the development of clinical AIDS than $CD4^+$ T cell counts. These discoveries facilitated the development of a rapid, inexpensive test to predict whether a patient would progress to AIDS.

> “AIDS is not simply caused by the absence of an immune response, but is characterized by the presence of a chronic dysfunctional immune response”



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Moreover, they suggested that chronic activation of the immune system (as opposed to direct destruction of $CD4^+$ T cells by the virus) was linked to HIV pathogenesis. This idea was further strengthened by the realization that SIV viruses do not generally induce the development of AIDS-like diseases in their natural primate hosts, even though the viruses infect $CD4^+$ T cells and establish chronic infections. A key study by Guido Silvestri and colleagues in 2003 reported that T cell populations are essentially normal in sooty mangabey monkeys that are chronically infected with non-pathogenic SIV, despite high levels of viral replication in $CD4^+$ T cells. Notably, the monkeys had low levels of immune activation. These findings gave credence to a growing school of thought that an aberrant chronic immune response has a major role in the pathogenesis of AIDS.

Another crucial piece of evidence came from the findings of the SMART study group in 2006. This clinical trial showed that intermittent (as opposed to continuous) antiretroviral therapy (ART) in patients infected with HIV caused increased death from non-AIDS-related causes, secondary to immune activation.

Although by the mid-1990s it had become clear that chronic immune activation was a hallmark of progressive HIV infection, the mechanistic basis of this was still not understood. In 2006, Jason Brenchley et al. reported that microbial translocation from the gastrointestinal tract occurs in HIV-infected individuals and results in increased circulating levels of lipopolysaccharide (LPS). Similar findings were made in rhesus macaques infected with pathogenic SIV. Importantly, increased levels of LPS in the blood circulation correlated with higher activation of both the innate and adaptive immune systems. This suggested that loss of mucosal barrier function (most likely as a result of acute $CD4^+$ T cell depletion) leads to systemic immune activation.

However, even today, it is still not clear exactly how chronic immune activation occurs during pathogenic HIV infections. Other proposed mechanisms include immune responses to the virus and opportunistic infections, or loss of specific $CD4^+$ T cell subsets that are important for immune homeostasis. Importantly, recent work has also indicated that markers of systemic inflammation, particularly plasma levels of IL-6, are in fact better predictors of clinical outcome than levels of T cell activation.

In summary, through time, it has become clear that AIDS is not simply caused by the absence of an immune response, but is characterized by the presence of a chronic dysfunctional immune response, which drives disease progression by causing tissue damage and organ failure.

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