AIDS Pathogenesis: A Finite Immune Response to Blame?

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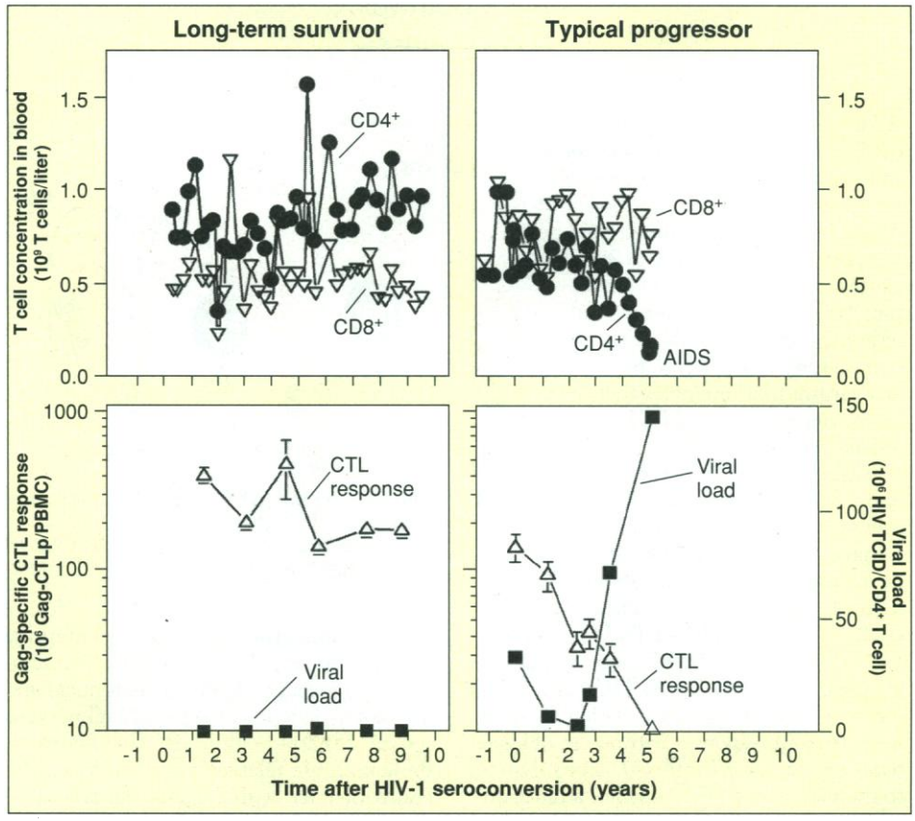
Exactly how the human immunodeficiency virus type–1 (HIV-1) induces acquired immunodeficiency syndrome (AIDS) remains controversial (*1*). Most individuals infected with HIV-1 remain disease free for many years and, during this time, maintain relatively stable numbers of $CD4^+$ T cells, strong cytotoxic T cell (CTL) responses, and low numbers of HIV-1–infected cells in the blood, all indicators that the virus is under substantial immune control. At some point, however, the immune system falters, and most infected individuals progress to develop the symptoms of AIDS (*2–4*).

Why does the immune system fail to control HIV-1 infection? Some believe that the immune response to the virus is actually harmful (*5*), whereas others have suggested that HIV-1 weakens the immune system by either increasing viral diversity (*6*) or causing immune dysregulation (*7*). Several studies have also implied that differences in viral pathogenicity may contribute to the development of AIDS (*8–10*).

In a report in this issue, Wolinsky and colleagues present results of a comprehensive study of six individuals who experienced different clinical courses of HIV-1 infection and use these results to discriminate among some of these theories (*11*). One of the hypotheses they test is the "antigenic diversity threshold" theory, proposed in 1990 by Nowak and colleagues to explain the breakdown of the immune system during HIV-1 infection (*6*). This mathematical model has since been adapted and improved and can be summarized as follows: The cellular immune response against HIV-1 is directed to both conserved and variable epitopes. Assuming that the CTL response to conserved epitopes cannot completely eradicate HIV-1, the response against variable epitopes is required to achieve a steady-state number of $CD4^+$ T cells and HIV-1 viral load. This response to variable epitopes will cause an ever increasing antigenic diversity of the virus population, which will dilute the immune response, and thus "befuddle the patients immune system, which becomes less effective." Moreover, the continuous mutational escape from CTLs will direct the immune response "to weaker and weaker (subdominant) epitopes," away from the initially recognized immunodominant epitopes (*12, 13*).

Because of the intellectual appeal of this antigenic diversity theory, it has attracted significant attention and has even guided discourse in the field. One of its most specific and to some extent testable predictions is that increasing antigenic diversity underlies the development of AIDS (*6*). In the last few years several laboratories have studied this issue, and it is now clear that this aspect of the hypothesis is refuted by experimental results. Wolinsky and his co-workers found no evidence for a threshold in viral diversity occurring at the same time as the precipitous decline of $CD4^+$ T cell numbers in four patients who were progressing to AIDS. In fact, the two patients who progressed the fastest had high levels of plasma HIV-1 RNA with very limited viral diversity, whereas the two slowly progressing individuals had high levels of viral diversity, results in agreement with other cross-sectional and longitudinal studies (*14, 15*).

Another interesting observation of Wolinsky and co-workers is that the accumulation rate in viral RNA of nonsynonymous mutations (those that result in amino acid changes), when compared with synonymous mutations, was higher in slow progressors than in rapid progressors. The accumulation of such nonsynonomous mutations during the asymptomatic period indicates that there are selective constraints on the viral quasi species. Recently, in a study done in the Amsterdam Cohort, Goudsmit's group also reported a correlation between the accumulation of nonsynonymous (but not synonymous) mutations and the length of the immunocompetent period (*15*). The selective force may well be the patient's HIV-1–specific CTL response, as Wolinsky *et al.* suggestively show that strong CTL reactivity against the HIV-1 envelope protein correlated well with amino acid changes in a well-defined epi-



Natural history of HIV-1 infecton. Long-term survivors of HIV infection maintain normal $CD4^+$ and $CD8^+$ T cell numbers, persistent Gag-specific CTL responses, and low numbers of $CD4^+$ T cells infected with HIV-1. Individuals who eventually show symptoms of disease (typical progressors) have relatively stable numbers of $CD4^+$ T cells during a variable latency period, which are disturbed by decline of HIV-1–specific CTL responses coinciding with increasing viral load, leading to total collapse of the immune system and inevitable development of AIDS. TCID, tissue culture infectious dose; PBMC, peripheral blood mononuclear cell; CTLp, CTL precursors. [Adapted from (*2*)]

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tope that is a potential target for CTLs. Moreover, CTL responses were strongest in the slow progressors and nearly undetectable in the rapid progressors. Taken together, one may conclude that CTL responses put selective pressure on the virus and cause increasing viral diversity (*16*), and that sustained HIV-1–specific CTL responses are associated with a favorable clinical course (*2*–*4*) and not with rapid progression per se (*5*). In fact, the rapid progressors in Wolinsky's study had very poor CTL responses. Although in the six patients they studied no differences in viral pathogenicity were observed, viral phenotype may nevertheless be relevant for disease progression.

These intriguing new results leave us with several unanswered questions. Foremost, we need to understand what disturbs the quasi steady state of stable, asymptomatic HIV-1 infection (see the figure). It has been suggested that the enormous turnover of $CD4^+$ T cells eventually exhausts the lymphopoietic system, and that there is no need to invoke other immunological mechanisms for the onset of AIDS (*17*). We believe that sustained CTL responses are required to eliminate HIV-1–infected cells and to keep the viral load as low as possible. Progression to AIDS may then be precipitated by gradual perturbation of cellular immunity, through the decline of $CD4^+$ T cell numbers and through impairment of T cell function, both of which are likely to affect the ability of the immune system to control HIV-1 infection (*2*, *7*, *18*). HIV-1 RNA levels are strong predictors of disease progression. Nevertheless, large numbers of productively infected cells, not free virus in blood, will harm the immune system the most. Therefore, efficient control of the number of HIV-1–infected cells is of utmost importance. HIV-1 may be best contained by combining immunotherapy with antiviral drugs.

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p75^{NTR}: A Receptor After All

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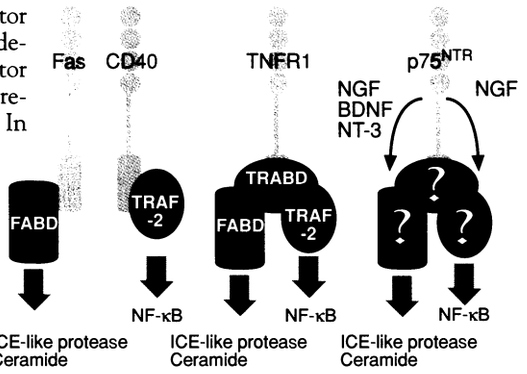
The 75-kD neurotrophin receptor (p75^{NTR}) has been an enigma for a decade. It was among the first growth factor receptors to be cloned (*1*), but until recently its function remained obscure. In a report in this issue of *Science*, Carter *et al.* (*2*) provide evidence that p75^{NTR} mediates functional responses of Schwann cells to nerve growth factor (NGF) by a mechanism that resembles that of tumor necrosis factor (TNF) and related cytokines.



Signal transduction by the p75^{NTR}-TNF receptor superfamily. A model for p75^{NTR} signal transduction, based on a simplified rendition of the models proposed by Goeddel and co-workers for other members of the receptor superfamily (*13*).

Although p75^{NTR} was originally characterized as an NGF receptor, it was shown subsequently to have similar affinity for all the neurotrophins, including brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5, and NT-6 (*3*). p75^{NTR} fell into disrepute after the discovery of TrkA, TrkB, and TrkC receptor tyrosine kinases, which mediate neurotrophin responses without an obligate requirement for p75^{NTR} (*4*). Contributing to the view that p75^{NTR} was not a functionally important neurotrophin receptor was the initial perception that mice with gene-targeted p75^{NTR} mutations had relatively minor neurological deficits. More extensive analysis has revealed that these mice actually have rather widespread anatomical and functional deficits of the peripheral nervous system (*5*), and, although the brains of these mice are relatively normal, so are the brains of mice with targeted mutations of the TrkA, TrkB, and TrkC receptor genes (*6*). Such results left investigators to ponder the apparent redundancy of mechanisms regulating neural development.

Accumulating evidence has indicated that p75^{NTR} may modulate the function of Trk receptors. p75^{NTR} enhances the affinity of TrkA for NGF (*7*), perhaps as a result of a direct physical interaction of the two receptors (*8*), and p75^{NTR} may also influence activation of TrkB and TrkC receptors (*9*).

Only recently, however, has it become clear that p75^{NTR} may trigger cellular responses without participation of Trk receptors at all. Schwann cells are an obvious cell system in which to seek p75^{NTR}-mediated signaling events. These glia express substantial amounts of p75^{NTR}, particularly during development and after nerve injury in the adult (*10*). Schwann cells do not express functional Trk receptors, yet they respond to NGF with increased expression of the adhesion protein L1 and enhanced migratory activity (*11*). These findings have received little attention, perhaps because, absent any known capacity for p75^{NTR} signal transduction, they have seemed implausible.

When the sequence of p75^{NTR} was first described, the structure of the encoded protein was unique, and the short cytoplasmic domain of the receptor seemed poorly suited to signal transduction. Subsequently, however, many structurally related receptors were characterized, including two TNF receptors (TNFR1 and TNFR2), CD40, and Fas. These other receptors, all bearing similarly puny cytoplasmic domains, clearly convey potent signals to the cell (*12*). Understanding of the mode of action of p75^{NTR} has benefited substantially from studies of the signaling mechanisms of the TNF receptors, CD40, and Fas. These receptors couple, to varying extents, to two parallel signaling pathways leading, respectively, to apoptotic cell death or activation of the transcription

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