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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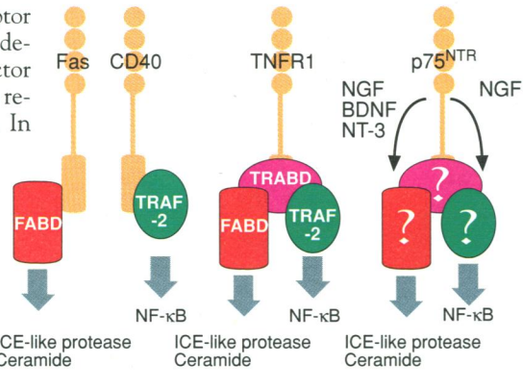
p75^{NTR}: A Receptor After All

Mark Bothwell

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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factor NF-κB (*13*, *14*). TNFR2 and CD40 signal NF-κB activation more prominently than cell death. The cytoplasmic domains of these receptors associate with structurally related cytoplasmic proteins, TRAF1 and TRAF2, and, for CD40, also TRAF-3 (*15*). Fas signals apoptosis, mediated by the association of its cytoplasmic domain with a cytoplasmic protein, FADD. TNFR1, signals both apoptosis and NF-κB activation, mediated by the association of its cytoplasmic domain with the protein TRADD. TRADD associates with both TRAF2 and FADD, apparently accounting for the capacity of TNFR1 to activate both the apoptotic and NF-κB pathways. Interactions of TNFR1 and Fas with TRADD and FADD are mediated by a sequence motif known as a "death domain," present in all four proteins (*13*, *14*).

The recognition of a death domain motif within $p75^{NTR}$ led Rabizadeh *et al.* to examine whether $p75^{NTR}$ might promote apoptotic cell death. Evidence to support such an activity was obtained in several neuronal cell lines (*16*). Involvement of $p75^{NTR}$ in apoptotic cell death has also been reported for two populations of developing neurons (*17*). Enhanced conversion of sphingomyelin to ceramide, which accompanies TNF-induced apoptotic cell death, has been demonstrated in response to activation of $p75^{NTR}$ by NGF, BDNF, or NT-3 in several cell lines (*18*). The new study of Carter and co-workers extends these findings in an important way by directly demonstrating that $p75^{NTR}$ dramatically contributes to NF-κB activation and does so in a cell system that responds to NGF with a physiologically relevant response.

Two elements of functional complexity distinguish the neurotrophin response system from that of TNF. Firstly, NGF-induced tyrosine kinase activity of the TrkA receptor negatively regulates the capacity of $p75^{NTR}$ to mediate NGF-induced ceramide production. Thus, Trk function modulates $p75^{NTR}$ function, just as $p75^{NTR}$ function modulates Trk function. Second, although NGF binding to $p75^{NTR}$ induces ceramide production and NF-κB activation, BDNF and NT-3 binding to $p75^{NTR}$ do not induce NF-κB activation, but induce ceramide production even more effectively than does NGF. These results are difficult to understand if ceramide is the endogenous inducer of NF-κB activation, as is commonly presumed, and as Carter and co-workers assume in their new study. Recent studies suggest, however, that NF-κB activation is not downstream of ceramide production, but rather that ceramide production is a consequence of activation of ICE-like proteases in the alternative signaling pathway leading to apoptosis (*14*, *19*). A model that can reconcile these findings is one in which $p75^{NTR}$ signals through both FADD-like and TRAF-2–like pathways, with NGF activating both pathways, whereas BDNF and NT-3 activate only the TRAF-2–like pathway. The plausibility of nonequivalent action of the various neurotrophins is supported by the finding that an antibody against $p75^{NTR}$ inhibits NGF binding more effectively than binding of BDNF or NT-3 (*20*), suggesting that the neurotrophins bind to different sites on $p75^{NTR}$.

A key question remains: Do TRAF-2 and FADD themselves mediate $p75^{NTR}$ signaling, or are other structurally related proteins involved? The availability of dominant, negatively acting mutant forms of TRAF-2 and FADD will facilitate this analysis. The yeast two-hybrid technique has been instrumental in identifying signaling molecules interacting with other members of the $p75^{NTR}$-TNFR receptor family. It is likely that this approach will also help to unravel the $p75^{NTR}$ signaling system.

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Saturn's Rings: Life at the Edge

Carl D. Murray

The most spectacular ring system of the outer planets can also be a nuisance. The icy particles of Saturn's rings are so efficient at reflecting sunlight that the resulting glare makes it almost impossible to detect faint material lying close to the main ring system. However, over the last year astronomers were able to observe the Saturn system without the customary glare when the rings appeared edge-on as viewed from Earth. Some of the results obtained with the Hubble Space Telescope (HST) are reported in this issue (*1*–*3*). The most interesting images are those of the small satellites and ring features lying just beyond the main rings. They reveal a remarkably dynamic system with transient phenomena and a satellite inexplicably out of position. Something strange is happening.

It was Huygens (*4*) who first realized that Saturn's ring system appears to vanish twice every orbital period of 30 years as the Earth crosses the ring plane and the rings are viewed edge-on (see figure). As a result, ground-based discoveries in the Saturn system tend to occur at intervals of 14 or 16 years. Because our terrestrial viewpoint is changing as we orbit the sun, this last year has seen three Earth ring-plane crossings—22 May and 10 August 1995 and 11 February 1996—and one sun crossing on 19 November 1995. Although three spacecraft have now visited Saturn (Pioneer 11 and Voyagers 1 and 2), observations at times of ring-plane crossing are still vital, especially because they can provide unique viewing geometries for extended periods. For example, Hall *et al.* (*1*) discuss the spectroscopic detection of OH immediately above the main rings, an observation that can only be made at times of ring-plane crossing.

A recurring yet unexpected result common to many of the current observations is the importance of Saturn's F ring in attempts to understand phenomena as varied as the thickness of the rings and the temporary nature of some features. The F ring is a narrow, multistranded ring lying 3400 km beyond the edge of the main ring system

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