Perspective

T Cell Signaling

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THYMIC-DERIVED LYMPHOCYTES (T CELLS) ARE FUNDAMENTAL regulators of vertebrate immune function. Presentation of an antigen to such cells elicits the production of regulatory cytokines, which stimulate both antibody production and cellular defense mechanisms. Steady progress has been made in identifying the receptors on T cells that permit specific recognition of an essentially infinite variety of potentially injurious "nonself" molecules, and these studies have provoked investigation of a related question: how is the signal from the T cell antigen receptor transmitted to the cell interior? Hurley *et al.* (*1*) in this issue of *Science* present one of a series of analyses that are providing insight into T cell signal transduction mechanisms.

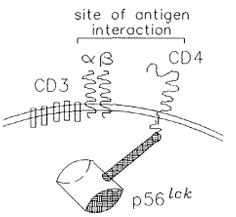
The antigen receptor on T cells is a heterodimer, most often composed of α and β chains (*2*). These two receptor polypeptides resemble antibodies in structure and interact with antigens that are presented to T cells as proteolytic digestion fragments associated with major histocompatibility complex (MHC) proteins on the surface of antigen presenting cells. The T cell receptor is associated with at least five other transmembrane proteins, collectively referred to as the CD3 complex (*3*). In addition, T cells can be fractionated into two subsets: those bearing the CD4 surface protein recognize immunogenic peptides associated with MHC class II proteins and those bearing CD8 molecules recognize immunogenic peptides associated with MHC class I proteins. The CD4 and CD8 molecules seem to form part of an antigen recognition complex that includes the αβ heterodimer and the CD3 polypeptides (*4*).

No consensus has emerged however regarding the nature of the signaling process that couples antigen recognition to changes in lymphocyte behavior. Biochemical changes that accompany receptor activation in other cells, including increased inositol phospholipid turnover, increased accumulation of cytosolic free calcium, and activation of protein kinases, also occur after T cell receptor stimulation (*5, 6*), but it has been impossible to demonstrate a cause-and-effect relation among these events.

Attempts to elucidate T cell signaling pathways are increasingly focusing on a lymphocyte-specific membrane-associated protein tyrosine kinase, $p56^{lck}$. First identified by virtue of its overexpression in a murine lymphoma cell line, $p56^{lck}$ is the product of a proto-oncogene (*lck*), which is closely related to c-*src*, and hence is a potential signal transduction element (*7*). Two pieces of evidence suggest the type of signaling event that may be mediated by $p56^{lck}$. First, expression of *lck* mRNA and of $p56^{lck}$ is altered by stimuli that induce lymphokine release from T cells (*8*). Second, $p56^{lck}$ is physically associated with the CD4 and CD8 molecules (*9*).

Hurley *et al.* (*1*) now demonstrate that the properties of $CD4{\cdot}p56^{lck}$ differ from those of $CD8{\cdot}p56^{lck}$. In particular, treatment of lymphoid cells with activators of protein kinase C provoked the dissociation of $p56^{lck}$ from CD4, apparently as a result of CD4 internalization, whereas similar treatment had little effect on $CD8{\cdot}p56^{lck}$ complexes, even in lymphoma cell lines that express both CD4 and CD8 simultaneously. As CD4 internalization apparently accompanies antigen stimulation (*10*), it may be supposed that an alteration in the subcellular distribution of $p56^{lck}$ typically occurs during the physiological activation of CD4-bearing lymphocytes.

These findings raise the possibility that $p56^{lck}$ may behave in a similar manner to growth factor receptor tyrosine kinases (*7, 11*). Brought into proximity with the T cell antigen recognition unit by CD4 or CD8 "chaperones," $p56^{lck}$ activity may increase to reflect receptor occupancy (see insert; $p56^{lck}$ shown as a mallet). In accord with this model, antigen activation induces tyrosine phosphorylation of the CD3 ζ chain (*12*), as does antibody-mediated cross-linking of CD4 (*13*). Subsequent internalization of CD4, but apparently not CD8, may serve to downregulate the signaling process.



This representation of $p56^{lck}$ function ignores those (admittedly rare) T cells that lack CD4 and CD8 surface molecules but which nevertheless appear capable of responding to antigenic challenge. In addition, $p56^{lck}$ is only one element in the T cell signaling repertoire. A second membrane-associated protein tyrosine kinase, the product of alternative splicing of transcripts from the *fyn* proto-oncogene, is also abundant in T cells (*14*). $p59^{fyn}$ is overexpressed in lymphocytes from a strain of mice (*lpr/lpr*) in which the CD3 ζ chain is constitutively phosphorylated on tyrosine (*15*). Thus, to the extent that CD3 ζ phosphorylation is an indication of the activation state of the T cell antigen receptor, $p59^{fyn}$ is a candidate signaling enzyme, although $p59^{fyn}$ does not associate with CD4 or CD8 (*9*). Phosphotyrosine-specific phosphatases, which modulate the effects of protein tyrosine kinases, may also be regulators of T cell signaling. The CD45 molecule, found on lymphocytes and other white blood cells, consists of an intracellular phosphotyrosine phosphatase linked to an extracellular, presumably ligand-binding, domain (*16*). Since $p56^{lck}$ itself appears to be regulated by phosphorylation of a COOH-terminal tyrosine residue (*17*), an effect of CD45 on $p56^{lck}$ activity can be imagined and has already been demonstrated in cell lines selected for loss of CD45 expression (*18*).

Thus, the consequences of $p56^{lck}$ activation are at present speculative. Insight into the signaling circuitry of T cells must await the direct experimental manipulation of $p56^{lck}$ activity in antigen-responsive lymphocytes. The wait will not be long.

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