increasing either the adhesion of the T cell to its stimulating cell or the affinity of the receptor for its ligand. Recent evidence strongly suggests that CD4 and CD8 are actually physical components of the receptor and, as such, contribute directly to signal transduction during T-cell activation[18–21]. Signalling via TCR crosslinking is potentiated by about 100-fold when CD4 or CD8 are physically associated with the TCR[18,22]. This, in turn, means that when the TCR binds a class II MHC ligand, CD4 binding to the same class II MHC molecule lowers the threshold ligand concentration required for T-cell activation by 100-fold. This effect is of such a magnitude as to make it easy to understand why $CD4^+$ T cells recognize class II MHC ligands and $CD8^+$ T cells recognize class I MHC ligands. As CD4 and CD8 both physically associate with the TCR and contribute so strongly to signal transduction, it is in my view more appropriate to regard these molecules as coreceptors than as accessory molecules.

The studies discussed here extend the evidence for this coreceptor function from mature T-cell antigen recognition to intrathymic T-cell development. CD4 is essential for clonal deletion by class II MHC ligands in one set of experiments[7,8], and coreceptor expression is dictated by TCR specificity for thymic MHC molecules in the other[4–6].

These studies also show that it is the specificity of the TCR that dictates coreceptor expression, rather than the coreceptor dictating TCR specificity for MHC class. It makes sense for the specificity of the TCR to govern coreceptor expression, as the TCR is the variable antigen-recognition element that must control the behaviour of the cell on which it is expressed. How the TCR dictates coreceptor expression depends on which model of T-cell ontogeny turns out to be correct. I prefer models in which the two coreceptors transduce distinctive signals during positive selection in double-positive cells. These signals would share the property of inducing T-cell maturation, but would differ in that CD4 signals would programme the cell to repress CD8 expression, and vice versa. These distinctive signal-transduction systems might also account for the functional distinctions between $CD4^+$ and $CD8^+$ T cells.

Questions for the future

Many issues regarding T-cell development remain to be resolved. Among these are the sequence in which positive and negative selection occur, and at which stage in T-cell maturation. To validate the results obtained using transgenic mice, further experiments, especially those using TCR genes derived from class II MHC-restricted T-cell receptors, will be needed. The postulated differences in signalling for the CD4 and CD8 coreceptors must be tested experimentally. The location in which selective events occur is also important. Using monoclonal anti-receptor antibodies, this problem should be approachable by morphometric analysis of thymic sections, especially from transgenic mice.

Finally, all studies of thymic selection raise a fundamental question: how is it possible to select for maturation T cells that have the potential to recognize foreign antigen only if it is presented by self-MHC molecules, when the foreign antigen is not present? Furthermore, these same cells must be unable to respond to self-antigens presented by self-MHC. Note that about 99 per cent of T cells die during intrathymic development, probably because only rare cells meet these stringent criteria.

Two explanations for this aspect of T-cell development have been proposed[23,24]. One is that positive selection is more permissive than negative selection, allowing TCRs with low affinity for self-MHC to be positively selected but not clonally deleted. Alternatively, the MHC molecules on thymic epithelium may present a set of self peptides unique to this site and specialized for driving positive selection. This model would be strongly supported if it could be demonstrated directly that self-MHC in the thymic cortex presents peptides that differ qualitatively from those presented by self-MHC in the thymic medulla and peripheral tissues.

T-cell development, and the selection of the TCR repertoire in the thymus, must be regarded as very complex processes. Nevertheless, new techniques and methods of analysis are gradually illuminating this critical and fascinating area, and it is hoped in the near future even non-immunologists will find the subject freed of its pervading mysteries. □

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Charles A. Janeway, Jr is in the Department of Pathology and Biology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut 06510, and is visiting scientist at the Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts 02129, USA.

Daedalus

Jogging on the spot

JOGGING, says Daedalus, is a most exhausting and unpleasant activity. It does not use up enough energy to burn off any significant amount of fat, and must benefit the body by some indirect effect. One such effect is the 'oxygen-debt' induced by strenuous exercise. The hard-working muscles outrun the lungs, and the glucose in the bloodstream is metabolized faster than oxygen can be breathed in to burn it completely. Instead, it is oxidized incompletely, to lactic and pyruvic acids. These are burnt off later, as post-exertion panting repays the oxygen-debt.

Daedalus suspects that the benefits of jogging are entirely due to regular oxygen-debt. So he is seeking to impose it on the body without the pain and strain of heavy exercise. Partial suffocation might do the trick, but is probably even more unpleasant than jogging. A neater chemical alternative would be to drink a flavoured syrup of ethyl lactate and pyruvate. These esters are hydrolysed on digestion to lactic and pyruvic acids, and of course (as a useful bonus) alcohol. Imagine the appeal of DREADCO's lactate liqueur which makes you fit as it gets you drunk! As it doesn't even contain alcohol as such, it should not attract excise duty, either.

But biochemistry is seldom that simple, and Daedalus may have to imitate the effects of exercise more indirectly. DREADCO's biochemists are immobilizing the enzymes of muscle glycolysis on a suitable porous substrate, so that blood pumped through it will be transformed just as in an exercising muscle. Packed into a small tubular reactor, with cooling-fins to dissipate the heat generated, it would form an 'artificial muscle' that could be plumbed directly into the circulation by standard transfusion techniques. Not everybody enjoys sticking needles in their arms; but once that has been done, the user of DREADCO's artificial exercise machine need only switch on the pump, and lie back in a state of induced exhaustion while the obliging machine exercises for him. A simple flow-rate control will enable him to vary his virtual exertion from a gentle trot right up to a sustained Olympic sprint far beyond his real capacity.

At last the grim agony of physical endeavour can be abandoned; the obligatory fashionable garments and stylish shoes can be thrown away, the risks of overexertion forgotten, and the life of the mind cultivated once more. For the ultimate combination of laziness and decadence, artificial exercise might best be taken while watching pornographic videotapes. The heavy breathing induced by oxygen-debt would fit neatly into the mood of the occasion.

David Jones