(the intermediate affinity, tolerogenic ligands).

In that the T cells no longer respond to a normally stimulatory peptide antigen, they have become anergic. But this state differs from that induced by T-cell stimulation in the absence of a costimulator. In the latter case, T-cell responses can be restored by adding an exogenous source of costimulation, such as allogenic spleen cells or anti-CD28 antibody[6], whereas, when suboptimal peptides are used, exogenous costimulation does not restore the response. Clearly then, these two types of anergic cells differ, which must result from the difference in signals transduced by the T-cell receptor upon engagement of ligands of greater or lesser affinity.

How then are we to understand the nature of the signals given by the analogue peptides that result in the induction of anergy? Simply reducing the number of T-cell receptors engaged cannot account for the observations, because limiting amounts of the fully stimulatory peptides would have the same effect. I can envisage two possible mechanisms that could account for a differential signal. One is that the affinity of the receptor–MHC–peptide complex is now sufficiently low that the complex is short-lived; the other is that conformational change in the T-cell receptor may be required for efficient signal transduction, perhaps to allow interactions with the coreceptor, CD4 or CD8, and that the binding of the analogue peptides does not induce the change in conformation.

In either case it is possible, with appropriate handwaving, to suggest that the signal transduced by the T-cell receptor complex may be different to that transduced when it is fully engaged. Exactly how these signals differ is less clear. Production of inositol phosphates in the T cells, an indicator of the activation of a signalling pathway required to induce the influx of Ca^{2+}, is not increased on stimulation with the suboptimal analogues (although it can be argued that this assay is not sensitive enough to pick up the small amount of inositol-1,4,5-P_3 that would be required to induce a Ca^{2+} flux[11]). A measurement of intracellular Ca^{2+} itself would have been useful in dissecting the signalling events after stimulation with suboptimal peptide analogues, as cyclosporin A, which inhibits the Ca^{2+}-dependent signal transduced by the T-cell receptor, inhibits the establishment of the anergic state. This observation, which at face value is inconsistent with the failure to see increased levels of inositol phosphates in the T cells, may imply either that calcineurin, which is the target for cyclosporin A inhibition[12], is constitutively activated in the T-cell clones used by Sloan-Lancaster *et al.* and does not require a Ca^{2+} signal, or that the partial signal given by the suboptimal peptide analogues results in the production of enough inositol-1,4,5-P_3 to initiate a Ca^{2+} flux but too little to be detected by the assay used.

Whatever the mechanisms, the ability of T cells to be rendered anergic by suboptimal ligands poses both an opportunity and a problem. The opportunity is that potentially disadvantageous immune responses to defined epitopes, say in allergic responses, may be regulated by administering appropriate analogue peptides to anergize potentially responsive T cells. The problem is in understanding how any of our T cells manage to make responses at all. The nature of positive selection of T cells during thymic maturation supposes that there are low-affinity interactions, presumably mediated by self-MHC molecules complexed with some or other self-peptides, which signal to thymocytes that they express a functional receptor and which rescue the thymocytes from programmed cell death. All T cells therefore have a specificity which can be described as 'slightly different from self'. So are all of our T cells rendered anergic by self-antigens?

The effect of suboptimal peptide ligands shows that for T cells, as for humans, the process of recognition is a complex one, being composed of both seeing and perceiving. A fascinating insight into human perception comes from the study of agnosia, a condition in which the patient can see an object, and indeed describe it in detail (a hand-shaped sack with five pouches), while not being able to identify it (a glove). The anergy induced by suboptimal peptides is similar in that the T cells can 'see' the peptide (the receptor can bind the MHC–peptide complex) but not recognize it (the T cell does not make an effective response). Because failure of recognition is associated with partially stimulatory analogues rather than the cognate antigen, perhaps we have the case of the T cell who mistook his mother-in-law for a hat[13]. □

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1. Sloan-Lancaster, J., Evavold, B. D. & Allen, P. M. *Nature* **363**, 156–159 (1993).
2. Kappler, J. W., Roehm, H. & Marrack, P. *Cell* **49**, 273–280 (1987).
3. von Boehmer, H. *A. Rev. Immun.* **8**, 531–556 (1990).
4. von Boehmer, H. *Immun. Today* **13**, 454–458 (1992).
5. Linsley, P. S. *et al. J. exp. Med.* **173**, 721–730 (1991).
6. Harding, F. A., McArthur, J. G., Gross, J. A., Raulet, D. H. & Allison, J. P. *Nature* **356**, 607–609 (1992).
7. Mueller, D. L. *et al. A. Rev. Immun.* **7**, 445–480 (1989).
8. Schwartz, R. H. *Science* **248**, 1349–1356 (1990).
9. DeSilva, D. R., Urdahl, K. B. & Jenkins, M. K. *J. Immun.* **147**, 3261–3267 (1991).
10. Evavold, B. D., Williams, S. G., Hsu, B. L., Buus, S. & Allen, P. M. *J. Immun.* **148**, 347–353 (1992).
11. Kuno, M. & Gardner, P. *Nature* **323**, 310–314 (1987).
12. Schreiber, S. L. & Crabtree, G. L. *Immun. Today* **13**, 136–142 (1992).
13. Sacks, O. *The Man Who Mistook His Wife for a Hat* (Picador, London, 1986).

DAEDALUS

Heavenly music

A VENTRILOQUIST makes his voice seem to come from a distant source. Daedalus is now inventing a true, large-scale ventriloquism. It exploits those microwave frequencies that are feebly absorbed by water vapour in the air. His novel phased-array radar directs such an absorptively lossy beam upwards, and sweeps it angularly through the atmosphere.

The absorption of the beam heats and expands the air through which it travels. As the beam sweeps sideways, the expansion moves too. At some height in the atmosphere, determined by the angular sweep rate, the beam sweeps laterally at exactly the local speed of sound. The accompanying moving expansion launches a horizontal sound wave into the atmosphere at this precise height. If the sideways sweep is accelerated, the sonic height moves steadily downwards, tilting the sound beam down towards the ground. So by sweeping a spatially audio-modulated beam sideways, while updating it continuously at the trailing edge, Daedalus can create a disembodied voice which speaks from the sky.

The primary interest is military. The US army attacked General Noriega with a non-stop barrage of deafening rock music; the FBI used similar tactics in the Waco seige. The ghastly sonic barrage maddened its own side as well. Ventriloquial radar solves this problem: it makes no noise itself. Aimed into the sky, the silent beam can target any site within many kilometres, and stun it with kilowatts of accurately directed rock music. With enough computer power, it could be trained on a moving target such as an aircraft, following it around the sky till its distracted crew abandoned their mission. They might even conclude that the deafening, sourceless voice was inside their own heads, and that they were succumbing to schizophrenia.

Civilian uses would soon follow. As a free-air public-address system, ventriloquial radar could beam a celestial sports commentary or a pop sound-track precisely down onto a stadium, while leaving the surrounding area in perfect peace. It could also launch horizontal signals at high altitudes for scientific purposes. Like the ocean, the atmosphere may have confining layers within which sound travels horizontally for vast distances. The transit time, frequency response and distortion imposed on such signals would neatly reveal a vast amount about the air through which they had travelled. David Jones