receptor) theories of antigen recognition by T cells, one published by Pernis and Axel[25] and the other by Raulet *et al.*[21] and elaborated by Tonegawa at Aspen.

Both rest on the premise that the γ gene plays an important part in the recognition of class I MHC molecules by cytotoxic T lymphocytes, and attempt to explain self tolerance (mature T lymphocytes fail to respond to cells bearing 'self' MHC molecules on their own) as well as MHC restriction (they will attack and kill cells bearing a combination of self MHC and foreign antigen). Tonegawa proposes that the γ chain is associated early in ontogeny with the β chain to give binding to self MHC, inducing cell proliferation and thus selection for self reactivity; later in ontogeny he envisages the γ–β dimer giving way to an α–β dimer with a much weaker affinity for self MHC, so that effective binding can occur only with the addition of antigen.

The Pernis–Axel theory is an ingenious effort at explaining not only self tolerance and MHC restriction but alloreactivity as well (T cells will recognize and kill cells bearing non-self MHC). They posit a tetramer composed of two β chains each associated with either a γ chain, to produce self recognition, or an α chain, to produce an antigen binding site; a rarer and more doubtful association of the γ and α chains is supposed to underlie alloreactivity in what, by imaginative use of arithmetic, the authors describe as a one-and-a-half-receptor theory of T-cell recognition.

An untested prediction of both theories is the existence of a fourth gene expressed only in T-helper cells and acting as the equivalent of the γ gene in the recognition of class II MHC molecules. But how well does either theory stand up to the available evidence on the molecular basis of antigen recognition by T cells? The phenomena the two theories were devised to explain are among the most important and problematic in cellular immunology, and the γ gene is undoubtedly the outstanding puzzle of molecular immunology, so it is worth pausing to consider whether each can really help resolve the other.

It remains debatable, for example, whether the limited diversity of the γ gene would be sufficient to allow the binding of the entire range of class I MHC molecules, which are the most polymorphic known to protein chemistry. The expression of γ transcripts at very high levels early in the ontogeny of the thymus is very striking, and a γ–β heterodimer as proposed by Tonegawa is not ruled out, though such evidence as there is suggests that β chains do not emerge at the cell surface until relatively late, when they are coordinately expressed with α chains and the universal T-cell marker T3[22,23,26], which is now known to be essential for the activation of T cells by antigen binding (see Fig. 2, in box).

There is, however, compelling evidence against the Pernis–Axel theory, which requires an association between γ and β chains for antigen recognition on mature T cells. Yagüe *et al.* in the Kappler–Marrack laboratory have investigated α and β gene-loss mutants of three independent T hybridomas, all recognizing the same combination of foreign antigen and MHC. The *V* segments, and probably the *J* segments, of both the α and the β genes of the three hybridomas are identical. The loss of either the α or β gene results in loss of recognition; fusion of an α loss mutant with a β loss mutant restores recognition. Thus the α and β chains of the heterodimer seem to be both necessary and sufficient for dual recognition of MHC and foreign antigen.

If the γ gene does not encode a part of the antigen receptor — and assuming that it is in fact expressed on the cell surface — what part might it be playing in the ontogeny of T cells? The prevailing view at Aspen was that the answer probably lies in a consideration of the much broader context of T-cell surface molecules that share their ancestry with immunoglobulin. The full extent of this family of molecules[11], whose growth has been charted at intervals in *Nature* by Alan Williams[27], has only recently begun to emerge from the sequences of genes encoding the surface molecules originally defined by monoclonal antibodies as differentiation markers of T cells; and it is especially relevant that two in particular, T8 (or CD8)[28] and T4 (CD4)[29], are now also known to belong to it. These two molecules are expressed respectively on lymphocytes recognizing class I and class II MHC molecules and are strongly implicated in precisely the kind of role imagined for the putative γ chain. Antibodies against T8 block cytotoxic responses, and those against T4 block T-cell help; accordingly it has been suggested that they contribute to the binding of antigen by T cells by recognizing the non-polymorphic determinant on the class I and class II MHC molecules. Some such role as an accessory recognition molecule is generally deemed plausible for the γ-gene product (assuming, again, that there is one). This would, however, make the γ chain the only known non-antigen-receptor molecule to be encoded by a gene that undergoes somatic rearrangement.

Moreover, it is unsettling that such molecular biology as has been brought to bear on the issue of accessory recognition molecules so far has succeeded in undermining somewhat the attractive schema I have just outlined. Golding *et al.* have transfected cells with a class II gene from which the exons encoding the non-polymorphic domains have been removed. If the binding of these domains by T8 reinforces the specific binding of the polymorphic determinants by the T-cell receptor, then this operation might be expected to abrogate specific recognition. But it does not: alloreactive T cells raised against cells bearing the intact class II molecule will still recognize the truncated one on the transfected cells. This could merely mean that T8 is not always necessary for recognition and binding; however Golding *et al.* have also shown that recognition of such cells is blocked by antibodies to T8, and this is very hard to explain if it is the conserved non-polymorphic determinants of the class II molecules that are involved in accessory recognition. On the other hand, the importance of T8 is clearly affirmed by these experiments and it remains possible that the interaction is with non-polymorphic portions of the polymophic domains.

Thus while the immunoglobulin family of lymphocyte surface molecules has clearly evolved for specialized interactions in cell–cell recognition, the molecular characterization of its various branches has so far failed to reveal exactly what those interactions are.

It is progress of a sort to learn how recognition of antigen by T cells is not mediated; next year perhaps the availability of cloned genes for all the known and putative recognition structures and the technology for transfecting cells with them will begin to offer some insight into how it is mediated. □

1. Robertson, M. *Nature* **312,** 16 (1984).
2. Hedrick, S.M. *et al. Nature* **308,** 153 (1984).
3. Chien, Y. *Nature* **312,** 31 (1984).
4. Saito, H., Kranz, D.M., Eisen, H.N. & Tonegawa, S. *Nature* **312,** 36 (1984).
5. Yagüe, J. *et al. Cell* **42,** 81 (1985).
6. Meuer, S.C. *et al. Nature* **303,** 808 (1983).
7. Arden, B., Klotz, J.L., Siu, G. & Hood, L.E. *Nature* **316,** 783 (1985).
8. Hayday, A.C. *et al. Nature* **316,** 828 (1985).
9. Winoto, A., Mjolsness, S. & Hood, L.E. *Nature* **316,** 832 (1985).
10. Yoshikai, Y. *et al. Nature* **316,** 517 (1985).
11. Hood, L.E., Kronenberg, M. & Hunkapillar, T. *Cell* **40,** 225 (1985).
12. Patten, P. *et al. Nature* **312,** 40 (1984).
13. Barth, R.K. *et al. Nature* **316,** 517 (1985).
14. Behkle, M.A. *et al. Science* **229,** 566 (1985).
15. Becker, D.M. *et al. Nature* **317,** 430 (1985).
16. Saito, H. *et al. Nature* **309,** 759 (1984).
17. Hayday, A.C. *et al. Cell* **40,** 259 (1985).
18. Murre, C. *et al. Nature* **316,** 549 (1985).
19. Le Franc, M.P. & Rabbitts, T.H. *Nature* **316,** 464 (1985).
20. Quertermous, I. *et al. Science* (in the press).
21. Raulet, D.H., Garman, R.D., Saito, H. & Tonegawa, S. *Nature* **314,** 103 (1985).
22. Collins, M.K.L. *et al. Proc. natn. Acad. Sci. U.S.A.* **82,** 4503 (1985).
23. Royer, H.D. *et al. Proc. natn. Acad. Sci. U.S.A.* **82,** 5510 (1985).
24. Heilig, J.S. *et al. Nature* **317,** 68 (1985).
25. Pernis, B. & Axel, R. *Cell* **41,** 13 (1985).
26. Ohashi, P. *et al. Nature* **316,** 606 (1985).
27. Williams, A. *Nature* **314,** 579 (1985).
28. Littman, D.R., Thomas, Y., Maddon, P.J., Chess, L. & Axel, R. *Cell* **40,** 237 (1985).
29. Maddon, P.J. *et al. Cell* **42,** 93 (1985).
30. Golding, H. *et al. Nature* **317,** 425 (1985).
31. Meuer, S.C. *et al. Cell* **36,** 897 (1985).
32. Ritz, J. *et al. Science* **228,** 1540 (1985).
33. Yanagi, Y. *et al. Nature* **314,** 631 (1985).
34. Reynolds, C.W., Bonyhadi, M., Herberman, R.B., Young, H. & Hedrick, S.M. *J. exp. Med.* **162,** 1249 (1985).
35. Siliciano, R.F., Pratt, J.C., Schmidt, R.E. & Reinherz, E.L. *Nature* **317,** 428 (1985).

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Corrigendum

In the article "Bridging the junctional gap" by Harry Goodall (*Nature*, 26 September, page 286), it was implied that the gap junction studies of N. B. Gilula and A. E. Warner used antibodies raised against junctional membrane preparations. In fact, their studies were conducted with antibodies raised against a 27K protein that was eluted electrophoretically from such preparations.