has been established that the bulk of the protein in the scrapie agent consists of a single molecular species (called PrP, for prion protein)[8]. PrP is a glycoprotein, of apparent relative molecular mass of 30,000, and has been highly purified and partially sequenced. When the complete sequence has been determined, it will be possible to synthesize the same sequence and test whether it has the same biological action as the natural agent. Only then will it be determined with certainty whether prions are both infectious and devoid of nucleic acids. When the synthetic molecule is available, antibodies to it could also be produced for titration of scrapie, and synthetic sequences of the corresponding gene could be constructed and used to investigate both the function of the PrP gene in the cell and the presence of the PrP gene in the host genome. It will also be important to determine the amino-acid sequences for myeloid proteins and compare them with PrP to establish the exact connection between amyloid plaques and the infectious agent.

The imminent resolution of many of these questions heralds an exciting era of biomedical advance. An intriguing area of scientific curiosity which has been impeded by forbidding technical problems has been transformed into a rapidly progressing and productive area of contemporary research. Already, the the immunological evidence available appears to provide support for the view that the amyloid plaques in the brains of scrapie-infected animals and humans with Creutzfeldt-Jakob disease are composed of arrays of prion proteins[9]. Soon we should know for certain whether prions do indeed represent a revolution in molecular biology and medicine, or if they are another manifestation of the complexity of interpreting molecular behaviour in the cellular microenvironment. □

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Immunology

Control of T-cell development

from Roland Scollay

OUR understanding of the control of the proliferation and early differentiation of T lymphocytes in the thymus gland is hazy, to say the least. Yet the thymus supports a large population of dividing cells[1] and about 30 per cent of its lymphocytes are replaced every day[2]. The hope that either one of the thymic hormones or interleukin-2 (IL-2) — a potent growth factor for mature stimulated T lymphocytes — would turn out to be the key factor for proliferation of the blast cells from which T lymphocytes are derived, has not been realized[3,4]. As a result the notion has arisen that growth factors are less important for proliferation than the interaction between blast cells and other non-lymphoid cells of the thymus. But two papers in this issue[5,6], showing IL-2 receptors to be on a subset of cells in the thymus, come as a faint ray of hope that IL-2 is the key.

About 80 per cent of the blast cells (15 per cent of all cells) in the murine thymus are the parents of the major population of small thymocytes in the cortex of the thymus. On their cell surfaces, they carry two antibody-defined markers associated with functional T lymphocytes[7]. The markers are Ly2 and L3T4, so the cells are classed 2^+4^+. Most of the other blast cells (about 3–5 per cent of all thymocytes) are 2^-4^-— that is they express neither Ly2 nor L3T4 and are generally felt to be precursors of, presumably, both cortical and medullary cells[7]. These 2^-4^-blasts are the predominant population in the embryonic murine thymus from day 12–16 or 17 of gestation, an observation which lends credence to their role as precursors[8].

It is on these 2^-4^-blasts that receptors for IL-2 have now been demonstrated. Ceredig *et al.*[5] use an antibody to the IL-2 receptors to show that about half the 2^-4^- blasts in both embryonic and adult thymus express the receptor, although those from the adult thymus (embryonic not tested), are slightly fewer in number and lower in affinity than those found on mature lymphocyte (Con A) blasts. They also demonstrate that the cells with IL-2 receptor are scattered throughout both the cortex and medulla of the thymus. Using different monoclonal antibodies, Raulet[6] finds a very similar distribution of the receptor on adult and embryonic blasts but, unlike mature lymphoid blasts which respond vigorously to IL-2, neither population of thymic blasts responds to IL-2 unless an additional stimulus (Con A) is added.

These data are relevant to a number of issues. First, it has generally been felt that 2^-4^-blasts are mainly confined to the outer cortex of the thymus, even though blasts in general, although more concentrated in the outer cortex, are widely distributed. The data from Ceredig *et al.*[5] show that the IL-2 receptor-positive 2^-4^- blasts are also widely distributed. Whether 2^-4^-cells occur in the medulla is still unclear, since it has not been established whether all the IL-2 receptor-positive cells are 2^-4^-, as both papers point out.

The second but related point concerns the heterogeneity of 2^-4^-cells. Other work shows that they are not a homogeneous population. Are receptor-positive and receptor-negative cells precursors for two pathways or lineages, or are they sequential stages of one (or more) pathway? The new data open up several interesting lines of experiment to answer such questions.

The third issue concerns the role of the receptor in cell differentiation. The receptors on thymic 2^-4^- blasts have relatively low affinity for IL-2, which perhaps accounts for the fact that the cells are not well stimulated by IL-2 alone. Unfortunately, there is no affinity data for the embryonic cells, which respond even less well to IL-2 alone, so it remains unclear whether this reflects a real difference in receptors or a response by the unkilled mature cells in the adult 2^-4^-preparation.

Nonetheless, the presence of the receptor in the embryo is important in interpreting the adult data. In general, immunologists associate IL-2 receptors with antigen- (or mitogen-) activated T lymphocytes and with mature cells that produce IL-2. The fact that before day 16 the embryo seems not to express antigen receptors[9] and that neither IL-2 producing cells nor cells of the usual (mature) IL-2 producing phenotype are detectable until several days later[8], suggests that the receptor on 2^-4^- cells may be operating quite differently from those on mature T cells. Indeed, the whole process within the thymus must be quite different, since the major, rapidly-dividing 2^+4^+ blast population, which presumably derives from the 2^-4^- blasts, is completely lacking the receptor[5,6] unlike any other population of activated lymphocytes. Perhaps we should not be unduly influenced by our knowledge of the activation process in mature cells in considering the significance of the IL-2 receptor on thymic cells and its presence on cells should not necessarily be taken as evidence that they are stimulated by antigen.

Some evidence of IL-2 production in the embryo would go far to establishing the relevance of the receptor. Without this, I find it too early to speculate on the receptor's role. But clearly, these experiments and the rapid increase in knowledge of the T-cell receptor brings us closer to an understanding of the secret workings of the thymus. One day a cocktail of factors added to a single T-cell precursor may allow us to observe the complete process of T-cell development in a test tube; but it may yet turn out that cell-to-cell interactions are essential. □

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