with the existence of such an association; melanoma metastases may lack HLA-DR antigen expression[6], and malignant mammary carcinomas may exhibit a deficiency in HLA class 1 antigen expression[7,8]. Certainly, future studies will test the generality of this association, although unfettered enthusiasm for such an all-encompassing theory on how tumour dissemination occurs must even now be tempered by the knowledge that suppression of MHC class 1 gene expression is not a universal characteristic of malignant tumours, nor are specific immune mechanisms the only host defence systems capable of modulating metastatic spread[9]. Indeed, increases in MHC class 1 gene expression may also be associated with metastatic capacity. Earlier studies have shown that expression of the D^k molecule may contribute to the metastatic behaviour of tumour cells[10], and a similar association between metastatic activity and expression of a gene homologous to MHC class 1 antigens has been established in another murine tumour system[11].

Recently the metastatic phenotype has been expressed by Ha-*ras* oncogene-transformed NIH 3T3 mouse fibroblast cells following transfection with genomic DNA isolated from a human metastatic tumour[12]. Acquisition of metastatic capacity correlates with the presence of discrete human DNA fragments, possibly representing a novel gene. Metastatic spread of the Ha-*ras*-transformed cells occurred in immunoincompetent (irradiated) nude mice but not in immunocompetent, histocompatible mice; the metastatic transfectants are capable of metastasizing both in immune depleted and in immunocompetent mice. Presumably the transfected gene confers some protection against the immune system and an attractive possibility is that this gene could turn out to be homologous to the putatively suppressogenic *H-2D*[1,11].

Unfortunately, such attempts to seek a single unifying explanation for the regulation of metastatic spread are probably oversimplifications; the complex multifactorial nature of the phenomenon suggests that answers obtained are likely to be as varied as the models used to address the questions. The true significance of Hammerling *et al.*'s report[1], along with other recent studies, may lie in the fact that these investigations represent the first applications of the techniques of modern molecular biology, such as gene transfer, to the central problem of clinical cancer and to a still major conundrum of tumour biology. □

1. Hammerling, G.J. *et al. Nature* **315**, 301 (1985).
2. Hui, K., Grosveld, F. & Festenstein, H. *Nature* **311**, 750 (1984).
3. Tanaka, K., Isselbacher, K.J., Khoury, G. & Jay, G. *Science* **228**, 26 (1985).
4. Sanderson, A.R. & Beverley, P.C.L. *Immun. Today* **4**, 211 (1983).
5. Fidler, I.J. & Hart, I.R. *Science* **217**, 998 (1982).
6. Albino, A.O., Lloyd, K.O., Houghton, A.N., Oettgen, H.F. & Old, L. J. *J. exp. Med.* **154**, 1764 (1981).
7. Fleming, K.A., McMichael, A., Morton, J.A., Woods, J.[1] & McGee, J.O.D. *J. clin. Pathol.* **34**, 779 (1981).
8. Natali, P.G. *et al. Cancer Res.* **43**, 660 (1983).
9. Barlozzari, T., Leonhardt, J., Wiltrout, R.H., Herberman, R.B. & Reynolds, C.W. *J. Immun.* **134**, 2783 (1985).
10. Katzav, S., Segal, S. & Feldman, M. *Int. J. Cancer* **33**, 407 (1984).
11. Olsson, L. *Fed. Proc.* **44**, 5414A (1985).
12. Bernstein, S.C. & Weinberg, R.A. *Proc. natn. Acad. Sci. U.S.A.* **82**, 1726 (1985).

Ian R. Hart is in the Imperial Cancer Research Fund Laboratories, PO Box 123, Lincoln's Inn Fields, London WC2A 3PX, UK.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

It is still unknown whether the recent findings are relevant to scrapie, illustrated here by a Cheviot sheep rubbing compulsively against a fence (photo courtesy of AFRC and MRC Neuropathogenesis Unit, Edinburgh, UK).

Scrapie

Persistently puzzling prions

from Tim Harris

MANY features of scrapie — a degenerative neurological disease of sheep and goats — including pathological similarities to the human degenerative diseases kuru and Creutzfeld-Jacob disease, suggest that it is caused by a 'slow' virus. The inability to find any typical virus particle consisting of nucleic acid and protein, however, coupled with the unusual resistance of infectivity to agents that normally inactivate nucleic acids, has led to some radical thinking about the nature of the scrapie agent. It has been proposed, principally by Stanley Prusiner and his colleagues[1,2], that a new type of proteinaceous infectious particle or 'prion' is involved in scrapie infection (for review, see ref.3). Two recent studies[4,5], one reported on page 331 of this issue[4], have now begun to produce molecular evidence that call this claim into question.

The evidence for the existence of prions stems largely from the fact that scrapie infectivity is proteinase sensitive, and that rod-shaped particles resembling amyloid fibrils are observed to co-migrate with infectivity in sucrose density gradients. SDS polyacrylamide gel electrophoresis of the proteins in this fraction (where infectivity is considerably enriched with respect to protein) has revealed a single polypeptide, PrP (prion protein) 27-30, of relative molecular mass 30,000; no nucleic acid has been found to be associated with it. Several models for the mechanism of prion replication have been put forward[6], the most heretical of which are that the protein is back-translated into nucleic acid (as yet achieved only by computer), or that PrP is a template for its own synthesis.

Recently, PrP has been purified and its partial amino-acid sequence obtained. The availability of this sequence for the design of oligonucleotide probes means that, if there is a messenger RNA for PrP, it would be only a matter of time before the isolation of complementary DNA clones. Given the degree of interest in the elusive scrapie agent, it is not surprising that this has happened sooner rather than later.

These molecular studies[4,5] present the cloning and sequencing of the mRNA for PrP 27-30 and show it to be the product of a single cellular gene. In addition, specific mRNA for PrP 27-30 is found in normal as well as in infected tissue. Can molecular biologists now heave a collective sigh of relief that the central dogma is still intact and that proteins do not self-replicate? For the time being the answer is probably yes, because unless the protein in infected tissue is subtly different to that in normal tissue (as has been found for certain cellular oncogenes), then it seems unlikely that PrP 27-30 is anything other than a normal cellular glycoprotein, the synthesis or degradation of which may be altered as a result of scrapie infection.

Nevertheless, the clarification of the origin of PrP 27-30 still does not explain the nature of the scrapie agent. In a negative way it does lend tacit support to the more conventional argument for a small scrapie-specific nucleic acid, suggested by the existence of different strains of the agent[7]. Whether this nucleic acid is contained in a small virus particle with a low particle-to-infectivity ratio, or is viroid-like and not encapsidated is not clear. But what is clear, now that PrP has been shown to be the product of a cellular gene, is that the hunt for the real scrapie agent is back with a vengeance. □

1. Bendheim, P.E. *et al. Proc. natn. Acad. Sci U.S.A.* **82**, 997 (1985).
2. Prusiner, S. *et al. Cell* **38**, 127 (1984).
3. Masters, C. *Nature* **314**, 15 (1985).
4. Chesebro, B. *et al. Nature* **315**, 331 (1985).
5. Oesch, B. *et al. Cell* **40**, 735 (1985).
6. Prusiner, S. *Scient. Am.* (10), 48 (1984).
7. Dickinson, A. & Fraser H.G. in *Slow Virus Infections of the Central Nervous System* (eds ter Meulen, V. & Katz M.) 3 (Springer, 1977).

Tim Harris is in the Division of Molecular Biology, Celltech Ltd, 250 Bath Road, Slough, SL1 4DY, UK.