suggestions that these two sialic-acid-binding proteins of the virus may have evolved from a common ancestor can safely be dismissed. The biological role of the NA activity is unclear. Without NA activity sialic acid remains on the viral glycoproteins where it binds the HA protein and leads to viral aggregation. Roles in transporting the virus through mucin and elution of progeny virus from infected cells have also been proposed.

Influenza virus is unusual because of the continual changes in the viral antigens that enable it to escape neutralization by antisera produced in earlier exposure, either through natural infection or through vaccination. Two modes of antigenic variation have been detected. Antigenic drift apparently results from point mutations in the virus genome which alter the surface glycoproteins in regions to which antibodies normally bind. Drift is associated with the familiar frequent recurrence of influenza epidemics. Much less frequently (1957, 1968, 1977), new virus strains appear in the human population by mechanisms (antigenic shift) which may involve genetic reassortment and/or transfer from an animal reservoir.

By examining the location of amino acid substitutions in a series of 'drifted' field strains and in three antigenic variants selected by growth in monoclonal antisera, Colman and colleagues have been able to propose the location of antigenic determinants on the NA. The antigenic sites are composed of loops connecting strands of β-sheet. They form a "nearly continuous surface" that "encircles the catalytic site" on the top of the NA. Although residues in the active site itself are conserved from strain to strain, the proximity of the variable loops to the site suggests that a significant part of the variable loops could interfere with any antibody contacting the active site cavity.

Although antibodies to the NA are not neutralizing, they modify the clinical symptoms of the disease. A similar analysis of antigenic regions has previously been done on the influenza HA to which neutralizing antibodies are directed[2]. In that case, sequences from the major epidemics since 1968 and a large number of monoclonal antibody-selected antigenic variants when interpreted on the X-ray structure of the HA, indicate regions likely to bind antibodies. Since amino acid substitutions have occurred in all the regions between each major human influenza epidemic, alteration in each of those regions of the HA may be required for the production of a new epidemic strain.

Because so much of the glycoproteins' surfaces have been observed to vary in antigenically important ways, no simple strategy for disease control has emerged. Perhaps more important for novel antiviral strategies may be the nearly ubiquitous requirement of animal viruses for an entry pathway mediated by low *p*H into internal cellular vesicles[9]. If, as is the case in influenza HA, a protein conformational change induced by low *p*H is required for entry[10], viruses may expose an Achilles heel only after uptake into cellular vesicles.

It is noteworthy that both viral glycoproteins have been solved by relatively novel crystallographic methods. The NA structure emerged only after data on two strains had been combined. One produced an uninterpretable map based on multiple isomorphous replacement phases, and in the other only a single isomorphous derivative and non-crystallographic 2-fold symmetry were available. An interpretable electron density map was produced only after the combination of all the data using real-space phase-refinement techniques[11,12]. In the case of the HA, the crystals contained both a non-crystallographic 3-fold symmetry axis and an unusually high solvent content (78 per cent by weight), allowing the structure to be solved by only a single heavy-atom derivative and non-crystallographic phase-averaging[12] incorporating solvent flattening. □

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1. Varghese, J.N., Laver, W.G. & Colman, P.M. *Nature* **302**, 35 (1983); Colman, P.M., Vorghese, J.N. & Laver, W.G. *Nature* **302**, 41 (1983).
2. Wilson, I.A., Skehel, J.J. & Wiley, D.C. *Nature* **289** 366 (1981); Wiley D.C., Wilson, I.A. & Skehel, J.J. *Nature* **289**, 373 (1981).
3. Ward, C.W. *Curr. Topics Microbiol. Immun.* **94/95**, 1 (1981).
4. Yewdell, J.W., Webster, R.G. & Gerhard, W.U. *Nature* **279**, 246 (1979).
5. Fields, S., Winter,G. & Brownlee, G.G. *Nature* **290**, 213 (1981).
6. Blok, J. & Air, G.M. *Biochemistry* **21**, 4001 (1982).
7. Deisenhofer, J., Colman, P.M., Epp, O. & Huber, R. *Hoppe-Seyler's Z. physiol. Chem.* **359**, 1421 (1976).
8. Wright, C.S. *J. molec. Biol.* **141**, 267 (1980).
9. Helenius, A., Marsh, M. & White J. *Trends biochem. Sci.* **5**, 104 (1980).
10. Skehel, J.J. *et al. Proc. natn. Acad. Sci. U.S.A.* **79**, 968 (1982).
11. Colman, P.M. *Z. Kristallogr.* **140**, 344 (1974).
12. Bricogne, G. *Acta crystallogr.* A32, 832 (1976).

Oncogenic intelligence

A new member of the *ras* family

from Peter Newmark

WITH the discovery that a human bladder carcinoma cell line (T24) contained a transforming gene closely related to the viral oncogene (v-Ha-*ras*) of the Harvey sarcoma virus of rodents, and that a transforming gene related to the oncogene (v-Ki-*ras*) of the Kirsten sarcoma virus was present in many human tumour cell lines as well as solid tumours, certain lines of research became inevitable.

One was to devise animal models in which the cellular *ras* genes were reproducibly activated. A start in that direction is reported on page 72 of this issue of *Nature*.

Another was to assign each of the human genes related to these viruses to particular chromosomes, a task that would have been completed by O'Brien *et al.* (*Nature* **302**, 839; 1983) who have now assigned four *ras* genes to four different human chromosomes — but for the discovery more recently of at least one more member of the *ras*-gene family.

The new member of the *ras*-gene family was identified during the study of human cancer cell lines whose transforming genes (detected by the NIH 3T3 cell assay) originally appeared to be unrelated to *ras* genes. Further studies have however revealed a relationship, if distant.

The strongest evidence of that so far has just been published from Michael Wigler's laboratory (*Proc. natn. Acad. Sci. U.S.A.* **80**, 2112; 1983) following up an earlier paper in the same journal (**80**, 383; 1983), and showing that the transforming gene of the neuroblastoma cell line SK-N-SH hybridizes to both v-Ha-*ras* and v-Ki-*ras*, though only weakly relative to the transforming genes of the T24 bladder carcinoma cell and various lung/colon carcinoma cell lines respectively.

What appears to be the same new transforming gene, christened N-*ras*, has also been found in two human sarcoma cell lines by A. Hall, C.J. Marshall, N.K. Spurr and R. Weiss (*Nature*, in the press) who had previously been unable to detect hybridization between the gene and either viral *ras* gene (C.J. Marshall *et al. Nature* **299**, 171; 1982). Now, however, the weak hybridization to both has been revealed. Evidence that the sarcoma-cell-transforming gene is the same as that in SK-N-SH neuroblastoma cell came from the hybridization of a probe derived from the former with the latter but not with any other sequence in human DNA.

It has been assigned to a chromosome other than those identified by O'Brien *et al.* (*op. cit.*) as containing the other *ras* genes.

Both groups provide evidence that no major rearrangement has been involved in the conversion of the normal gene into a transforming gene. Hall *et al.* also provide evidence that the major transcript of N-*ras* is similar in size and quantity in their sarcoma cell and in normal fibroblasts, indicating that increased expression cannot account for transformation.

Most probably, therefore, normal N-*ras* is converted into a transforming gene by mutation, possibly by a point mutation equivalent to that which distinguishes the T24 transforming gene from its normal counterpart and which, according to a recent prediction (*Nature* **302**, 842; 1983), disrupts a potential GTP or other nucleotide-binding site on the protein encoded in the gene. □

Peter Newmark is Deputy Editor of Nature.

0028-0836/83/180020-01$01.00