TUMOUR VIRUSES

Transforming Subunit

from our Cell Biology Correspondent

IT is now clear, chiefly as a result of the rigorous physico-chemical analyses made by Duesberg and his associates, that the single stranded RNA genome of the RNA tumour viruses is not a single polynucleotide chain but an aggregate of subunits. Each virion contains a single stranded RNA aggregate which sediments at between 60 and 70S and has a molecular weight of about $10–12 \times 10^6$; in denaturing conditions this genome is readily dissociated into its subunits, three or four molecules each of which sediment at about 36S and weigh about 3×10^6. Presumably the genes which cause transformation reside in one or more of these subunits, and in the December issue of the *Proceedings of the National Academy of Sciences* (**67**, 1673; 1970) Duesberg and Vogt report the electrophoretic separation of two chief classes of subunits, one of which is missing from the genomes of those avian sarcoma and leucosis viruses which cannot transform chick fibroblasts *in vitro*. This striking observation suggests, of course, that the genetic information necessary for the transformation of these cells resides in the class of subunits which is absent from non-transforming viruses.

Recent reports that gamma or ultraviolet irradiated Rous sarcoma viruses are able to reproduce in, but fail to transform, chick fibroblasts apparently prompted Duesberg and Vogt to compare directly the physical and chemical properties of the genomes of transforming and non-transforming avian tumour viruses. They thought that non-transforming mutants of sarcoma viruses, induced by irradiation, might be deletion mutants lacking a particular part or subunit of the genome of the parental transforming viruses. And for this reason Duesberg and Vogt also analysed the genomes of avian leucosis viruses, which, although able to induce leukaemia in chicks, presumably by transforming haematopoietic cells, fail to transform chick fibroblasts in culture.

The undenatured 60–70S RNAs of non-transforming mutants, and of transforming sarcoma viruses of different subgroups, were found to differ significantly in their electrophoretic mobilities. Polyacrylamide gel electrophoresis of these RNAs after dissociation into their subunits revealed the basis of these differences. All the RNAs from populations of transforming viruses contained two chief classes of subunits resolvable by electrophoresis, *a* and *b* subunits.

Presumably, different strains of viruses contain differing proportions of the two subunits and as a result their 60–70S RNAs have slightly different mobilities. By contrast the genomes of the four non-transforming sarcoma virus mutants and the three leucosis viruses examined were all found to lack *a* subunits. For example, Rous sarcoma virus B77, which transforms fibroblasts, has *a* and *b* subunits, whereas the non-transforming derivative NT B77 has only *b* subunits. Inevitably these experiments were carried out with RNAs isolated from large populations of the various viruses, and the results reflect only average RNA compositions. Nevertheless it seems clear that populations of viruses which fail to transform fibroblasts contain a preponderance of particles which lack *a* subunits and have in their place additional *b* subunits.

The only fly in the ointment is that it is possible that the presence of *a* subunits is a result rather than a cause of transformation. Because of this it would be extremely interesting to know the composition of the genomes of sarcoma virus particles liberated from cells transformed by the mutant Rous sarcoma virus isolated by Martin (see *Nature*, **227**, 998; 1970) which seems to have a temperature sensitive mutation in a virus gene, the functional expression of which is apparently required for the maintenance of transformation.

Duesberg and Canaani (*Virology*, **42**, 783; 1970) have also recently reported on another important aspect of RNA tumour virus biology, namely, the extent to which the RNA genome is transcribed into DNA by reverse transcriptases. By hybridizing the population of short DNA molecules made by disrupted Rous sarcoma viruses to RNA of those viruses, Duesberg and Canaani have shown that up to 75% of the base sequences in the viral RNA are transcribed; for technical reasons this is a minimal estimate. It seems probable therefore that *in vivo* the entire RNA genome may be transcribed into DNA.

OPERONS

Restricting Translation

"GENE action in bacteria is controlled by the interaction of a regulator protein molecule with DNA to prevent the transcription of RNA." This is the conclusion which has emerged from the research performed since Jacob and Monod proposed their theory of the operon in 1961. Their original idea was that the rapid switch on and switch off of bacterial genes could be controlled either at the level of transcription of DNA into messenger RNA, or by affecting the translation of mRNA into protein. But the finding that the lactose operon is controlled at transcription has proved so productive to exploit that the possibility that translational control might apply in other instances has been largely obscured.

Although there are tantalizing indications that some systems may be controlled to some extent at translation as well as at transcription, there has been no unequivocal demonstration of a system which relies on translational control instead of transcriptional control. Indeed, it has usually been assumed that any new system is controlled in what has become the conventional manner. But McClellan and Vogel have now resurrected the idea of translational control by showing (*Proc. US Nat. Acad. Sci.*, **67**, 1703; 1970) that translation of messenger RNA of the arginine system of *Escherichia coli* is reduced when the system is switched off.

The arginine system is somewhat bizarre in any case. The eight genes which specify the enzymes for synthesizing arginine from glutamic acid map at five separate loci on the *E. coli* chromosome, one locus comprising four genes, the others one each. But like the other operons of *E. coli*, where the genes coding for the enzymes of some metabolic pathway are all located together and are controlled as a functional unit, the arginine genes all respond to the same repressor protein. Mutants in the regulator gene (*arg R*) which codes for this protein cannot repress the arginine genes, and manufacture all eight enzymes without any control.

When *E. coli* cells are starved for arginine, the genes of this system are switched on and the corresponding messenger RNAs accumulate. (A similar event occurs with the tryptophan or histidine systems when bacteria are starved for tryptophan or histidine, respectively.) After allowing a certain amount of transcription, further synthesis of RNA can be inhibited by the addition of rifampicin, which inhibits the initiation of transcription. McClellan and Vogel have used this approach to distinguish the formation of mRNA from its translation, so that they can look separately at the two processes.

The activities of two of the enzymes of the system, acetylornithinase and ornithine transcarbamylase (which are coded by genes at different loci on the genetic map), were measured in either the presence or absence of arginine, with cells containing either the wild type *arg* R^+ or mutant *arg* R^- regulator gene. The surprising finding is that when arginine is present during translation, production of these enzyme activities is greatly reduced. But this reduction happens only in *arg* R^+ strains and not in *arg* R^- mutants. This means that the repressor protein coded by this gene is needed to restrict translation.

Arginine could interfere with translation in either of two ways; it might directly inhibit the translation of functional messengers, or it might cause degradation of accumulated arginine mRNA, thus preventing its translation. Experiments when mRNA was accumulated for some time in the presence of arginine, and its translation followed on