NEWS AND VIEWS

Accelerating Somatic Cell Genetics

THE standard technique for detecting linkage between human genes and assigning them to particular chromosomes involves correlating the chromosomal make-up with the biochemical properties of inter-specific hybrid cells. This approach to somatic cell genetics stems, of course, from the pioneering work of Watkins and Harris. They found not only that inactivated Sendai virus mediates cell fusion and, in Harris's words, converted "cell hybridization from an exercise in the exploitation of chance events to a method of general applicability", but also that when mouse and human cells are fused the hybrids preferentially lose most of their human chromosomes. If a normal human cell is fused with a mouse cell carrying some mutant biochemical marker and the hybrids are grown in conditions which do not support the growth of either parental cell, the hybrid should retain the human chromosome which carries the human gene that compensates for the defective murine function. A series of independently isolated clones of such hybrids should always have one human chromosome in common, that which carries the compensating gene. Once this has been established the hybrid cells can be analysed for a wide range of other human enzyme activities to see if any of these are always present and therefore carried on the same chromosome as the compensating gene. Using this basic approach Bodmer and his colleagues and Ruddle's group, for example, have established that the human genes specifying lactate dehydrogenase B and peptidase B are linked (*Nature*, **227**, 248; 1970), while Weiss, Green and Basilico have established that the thymidine kinase gene is probably located on a human chromosome of group *E*.

This mouse–human system, however, has its disadvantages. The hybrids emerge only slowly, and so experiments are protracted; the number of available genetic markers for the mouse cells is limited and the mouse cells in culture have as many as sixty chromosomes, which makes the identification of individual chromosomes in the hybrids extremely tedious. It will be no surprise therefore if in future the use of Chinese hamster cells, as described on page 329 by Kao and Puck, becomes widespread. Kao and Puck find that when these cells, which have only twenty chromosomes, are fused with normal human cells, the loss of human chromosomes is very rapid. Only a week after the fusion many of the hybrid cells have about twenty chromosomes and, moreover, eleven different auxotrophic markers of Chinese hamsters cell have already been isolated.

Kao and Puck have used three of these in an experiment which failed to establish any new linkage groups but proves beyond doubt the feasibility of their approach. They took Chinese hamster cells which were dependent for growth on the supply of either proline and glycine or proline and inositol, and fused them with normal human fibroblasts. The hybrid cells were grown in calf serum which does not support the growth of the human parental cells and in the presence of proline, but in the absence of either glycine or inositol. This condition selects, of course, for the retention of the human chromosomes which carry genes for the biosynthesis of glycine and inositol respectively. Once the hybrids had been isolated they were tested for the capacity to grow in the absence of proline. If the gene specifying the ability to make proline is on the same chromosome as either the glycine or inositol genes the hybrids should invariably grow in a medium lacking proline. In fact Kao and Puck found the proline requirement of their hybrids to be very variable. Out of fifteen hybrid clones able to grow in the absence of glycine only five could also grow in the absence of proline, while only seven of the forty-two clones able to grow without inositol could also grow without proline. Clearly there is no linkage between these genes in human cells, moreover the human lactate and malate dehydrogenase genes do not seem to be linked to the inositol gene.

It is disappointing that no new linkage groups have been detected but the technique of using doubly marked Chinese hamster cells and normal human cells holds great promise for the future. It means that possible linkage between two genes can be tested for directly, and there are eleven genes corresponding to the eleven auxotrophic markers of Chinese hamster cells that can immediately be studied by this approach. Kao and Puck's experiments have also thrown some light on the process of chromosome shedding. It seems that when cells with such disparate generation times as those of Chinese hamster cells, which divide every twelve hours, and human cells, which divide every twenty-two hours, are fused the condensation of the two sets of chromosomes becomes asynchronous. The faster growing partner seems to dominate the heterokaryon, and this leads by one or more mechanisms to the loss of the chromosomes of the laggard. From observations of individual cells Kao and Puck suggest that chromosome pulverization and the clumping of human chromosomes is related to the mechanisms of shedding and it seems likely that many of the human chromosomes are lost as groups rather than individually.

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