Gene Relocates During Differentiation

The polypeptide chains that make up antibody molecules seem to disobey a basic rule of modern biology. Rather than a single gene coding one polypeptide, different genes code for the two regions of each chain (SN: 10/19/74, p. 253). Now there is evidence that, during differentiation, one gene is moved adjacent to another antibody chain gene.

A central problem in immunology is how the immune system produces thousands of different antibody molecules to respond to the multitude of possible foreign toxins and pathogens. It would be impractical to have a separate gene for each molecule.

A partial explanation has been found in the combination of a constant portion of an antibody chain with one of a number of variable portions. Further, in ways yet unexplained, changes in the variable region give antibodies their characteristic property of combining specifically with whatever substance elicited their formation.

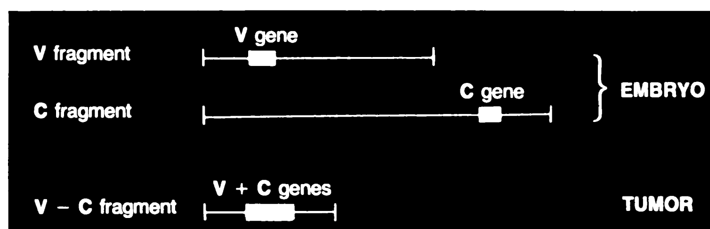
Three mechanisms have been suggested by which two genes could produce a single protein. The genes could move to adjacent positions in the chromosome before they are transcribed to a single messenger RNA, the messenger RNA produced from two separate genes could be joined before the protein is made or the final polypeptide chains could be enzymatically linked.

Twelve years ago W. J. Dreyer and J. Claude Bennett of the California Institute of Technology proposed that genetic material for the variable portion (V) of the chain combines with the constant region (C) gene during differentiation of antibody-producing cells. New evidence from the Basel Institute for Immunology in Switzerland supports this mechanism.

Nobumichi Hozumi and Susumu Tonegawa report in the October PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES that the location of the genes coding for one antibody molecule chain differs between embryonic and differentiated cells. The embryonic genes are some distance apart, while the genes from differentiated cells are contiguous.

Hozumi and Tonegawa analyzed DNA from embryonic mouse cells and from tumor cells derived from mouse bone marrow. Tumor cells, rather than normal adult cells, were used because all cells in a clone produce the same antibody. Antibody production of tumor cells is similar to that of normal cells.

The method of analysis was based on the specific binding of messenger RNA to the DNA sequence from which it was made. The researchers isolated messenger RNA for one of the polypeptide chains of an antibody and also a messenger RNA fragment, half as long, containing only the sequence for the constant region of the polypeptide chain. An enzyme was used to cut the mouse chromosomes into DNA fragments, which could be identified by their different lengths. They then mixed the DNA fragments with each of the messenger RNA molecules.



Genes for a single polypeptide are separate in embryo, but adjacent in tumor, DNA.

Two DNA fragments from the embryonic cells bound to the intact messenger RNA, and one of those fragments bound to the shorter RNA molecule. Therefore the gene for the constant region was in that DNA fragment.

Only one DNA fragment from the tumor cell, however, attached to either of the messenger RNA molecules. That DNA fragment was shorter than the embryonic DNA fragments that bound, but contained both genes (see diagram).

The researchers conclude that a region of DNA moves during differentiation. The details of how the mouse DNA changes position remain to be resolved.

Hozumi and Tonegawa propose that terminology, rather than a basic biological dogma, may need to be changed. There is an alternative to the concept of two genes producing one polypeptide chain. "Rather, there are two segments of DNA, one specifying the V region and the other specifying the C region," they write. "The gene is *created* by joining." □

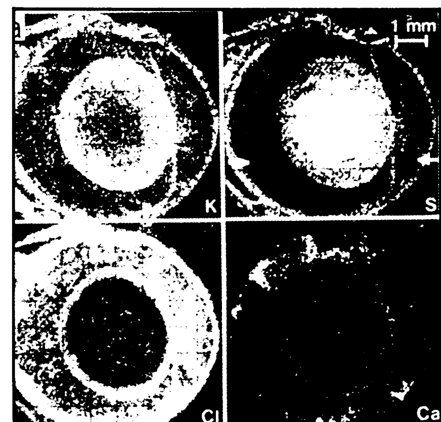
Element mapping in biological samples

Cutting, grinding, dehydrating or embedding a biological sample destroys valuable information about the spatial distribution of its components, so biological analysis demands techniques that can be applied to relatively undisturbed specimens.

A new biological tool has now been used to map out the elements present in a variety of specimens. In the Dec. 10 SCIENCE researchers report the use of the proton microprobe technique to analyze single strands of hair from poisoning victims, and eye and kidney specimens from rats. The technique was developed and applied by Paul Horowitz and Michael Aronson of Harvard University, Lee Grodzins and William Ladd of the Massachusetts Institute of Technology, Jean Ryan of the Lincoln Laboratory in Lexington, Mass., and George Merriam and Claude Lechene of Harvard Medical School.

In the new method a 2-million-electron-volt proton beam, brought out into the air, scans the sample. When elements in the sample are excited by the proton beam, they emit characteristic X-rays. An X-ray detector collects those rays, and the information can be stored in a computer memory. To produce a two-dimensional analysis, linear scans are made repeatedly across the sample and then displayed together on an oscilloscope screen.

The first biological samples examined



Microprobe map of four elements in eye.

were one-dimensional—individual strands of hair from victims of accidental mercury and arsenic poisonings. Along its length, each hair showed a peak of the toxic substance. The location of the peak, combined with the rate of hair growth, provided information about the time of the poisoning. Such analysis of hair might also be used to detect biochemical changes in a person.

The proton microprobe technique is especially applicable to understanding how mobile ions are distributed and concentrated in living tissue. The compartmentalization of ions is a central problem in physiology. Only living or frozen hydrated samples of tissue maintain their

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