Unexpected motif in genes for development

Surprising patterns are emerging from the analysis of genes that control animal development. Across a wide range of species, similar segments of DNA are being identified in a variety of genes that appear to direct cells into different developmental pathways. One such DNA segment, called the homeo box, appears in animals, from worms to humans, that have segmented body plans (SN: 7/14/84, p. 21). Now another segment has been identified; it is similar in developmental control genes of an unsegmented worm called a nematode and in those of a fruit fly. Unexpectedly, the piece of protein encoded by this DNA segment also matches a mammalian protein called epidermal growth factor (EGF).

Thus far, scientists can only speculate on what lies behind this shared motif. But the new results are expected to lead to further experiments exploring what triggers a cell to follow a specific pathway during development.

The analyses of the nematode and fruit fly genes were performed independently by scientists in the United States and in Great Britain. Each laboratory team identified within the control gene under study a repeated segment of nucleotides, DNA subunits, that encodes a sequence of about 40 amino acids including six cysteines, sulfur-containing amino acids. Both groups of scientists used a computer search to compare their data with the sequences of proteins previously analyzed. Each team concluded that its repeated DNA segment encodes a protein that has striking similarities to EGF, a molecule that stimulates the division and differentiation of some mammalian cells. The two sets of results are reported in the December CELL.

"These findings may help us learn about early steps of cell differentiation in the nervous system and, indirectly, give us insights into mechanisms underlying the onset of neoplastic, or cancerous, conditions," says Spyros Artavanis-Tsakonas, the Yale University biologist who with his colleagues identified the EGF motif in the fruit fly.

The Yale scientists were examining a fruit fly gene called Notch (because flies with an abnormality in this gene have notches in their wings). The gene is crucial to the correct developmental determination of nervous system and skin cells. When the gene is damaged, cells that should become skin tissue become nervous system tissue instead.

The new analysis of the Notch gene revealed that it encodes a protein containing 36 copies of an EGF-like segment. Other characteristics of the gene suggest that the protein encoded spans cell membranes, with the EGF-like segments extending out of the cell. Artavanis-Tsakonas and his colleagues Kristi A. Wharton, Kristen M. Johansen and Tian Xu speculate that the protein is involved in direct-contact interactions between cells. These interactions may be essential to the correct differentiation of immature cells into the precursors of nerve and skin tissue.

The other report of an unexpected EGF-like protein segment comes from research on a nematode gene called *lin-12*. The nematode has relatively few cells, enabling researchers to follow the path of each cell through the animal's development from egg to adult (SN: 1/1/83, p. 10). Abnormalities in *lin-12* result in an altered choice, for several sets of cells, between two developmental fates. "[This gene] appears to control developmental decisions made by cells in several different tissues, at different times, and between different developmental fates," says Iva Greenwald of the Medical Research Council Laboratory of Molecular Biology in Cambridge, England.

Greenwald reports that analysis of a portion of the *lin-12* gene shows 11 repeated units, each encoding a series of amino acids similar to EGF. In nematodes, as in fruit flies, the repeated amino acid segments are likely to be located outside a cell. Greenwald, too, suggests the protein is involved in intercellular communication.

"The results presented here indicate that *lin-12*, which has many of the formal genetic properties of [genes with homeo boxes], transmits developmental information via a very different molecular mechanism," Greenwald says.

Discovery of an EGF-like protein in relatively simple organisms indicates that the EGF motif must be an essential genetic building block, Artavanis-Tsakonas says, "because it has been carried almost intact from a common ancestor through eons of evolution into higher life forms."

The scientists do not suggest that the proteins encoded by the Notch and the *lin-12* genes necessarily perform the same role as EGF in mammals. Previous work in various laboratories has identified at least seven other proteins in mammals and one in vaccinia virus that contain EGF-like segments but whose functions appear unrelated to EGF's. The segments are all located in extracellular regions or on secreted proteins.

Artavanis-Tsakonas also suggests that this research will open new approaches to understanding EGF and how it influences cell growth. *—J.A. Miller*

Chemical clues to alcohol intoxication

The effects of alcohol intoxication on the activities of individual brain cells are not clear. Scientists are only beginning to work out the mechanisms of intoxication at a cellular and biochemical level (SN: 6/8/85, p. 357). An intriguing finding just reported may provide insight into alcohol's behavioral consequences.

Intoxicating doses of alcohol markedly affect the response of certain brain cells to two natural chemicals, acetylcholine and somatostatin-14. These substances, called neurotransmitters, carry signals between brain cells. The cells' responses to several other neurotransmitters — glutamate, gamma-aminobutyric acid (GABA), norepinephrine and serotonin — appear not to be significantly altered by alcohol intoxication, although the data for the last two substances are preliminary.

Jorge R. Mancillas, George R. Siggins and Floyd E. Bloom of the Scripps Clinic in La Jolla, Calif., first measured the electrical activity of several brain cells in each of 47 anesthetized rats. The cells are located in the hippocampus, a structure deep within the brain that plays an important role in learning and memory consolidation. After giving the rats alcohol doses equivalent to about four shots of bourbon for a man, the researchers injected a neurotransmitter into the brain area to see if the cells' electrical activity changed.

Acetylcholine prompts increases in cell activity, whereas somatostatin-14 causes a large drop in cell activity. These effects were enhanced in the alcohol-intoxicated rats, report the researchers in the Jan. 10 SCIENCE. Peak changes occurred 15 to 20 minutes after alcohol injections, and cell response returned to normal within 1 to 2 hours.

The effects of acetylcholine and somatostatin-14 appear to be closely linked. In an as yet unpublished study, the investigators find that somatostatin-14 naturally elevates responses to acetylcholine in the hippocampus. It is possible, they say, that alcohol enhances the effects of naturally occurring somatostatin in the hippocampus, which then "turns up" the responses of other cells to acetylcholine.

Although no similar effect was observed for GABA in alcohol-injected rats, J.N. Nestoros of McGill University in Montreal previously found that alcohol enhances the action of GABA in anesthetized cat brains (SN: 8/16/80, p. 102).

"It's a leap of faith to say our data is clinically relevant at this point," says Siggins, "but if the hippocampus is changed [during alcohol intoxication], it could explain lapses in memory and blackouts in some drinkers."

—B. Bower