acetylcholine receptor synthesis, and acetylcholine causes electrical activity and decreases synthesis."

Simply identifying the signals that turn genes on and off is only the first step, however. In the case of the gene for the acetylcholine receptor, CGRP and electrical activity must somehow be translated into messages inside the cell, which then have a specific effect on gene expression. Changeux points out that chemical second messengers fulfill this role, and that they might be different for the on and off regulation of the acetylcholine receptor gene.

"The positive signal, CGRP, simulates the production of cyclic AMP in muscle cells," he says. "It may be one of several regulating factors that have this effect. But the negative signal, electrical activity, acts through a different second messenger pathway. It seems to stimulate the production of diacylglycerol and inositol trisphosphate and raises the intracellular calcium concentration. But we still don't know whether it is through this pathway that the acetylcholine receptor gene is turned off."

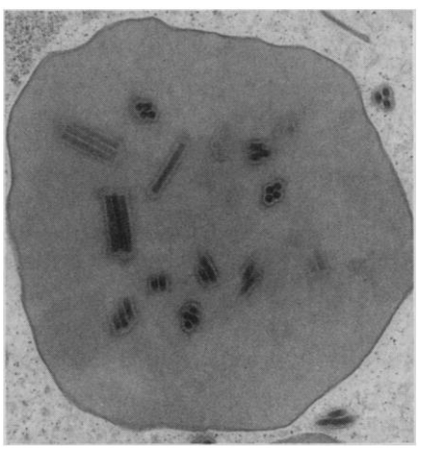
Changeux does not yet know when during development CGRP exerts its effect on the muscle cell gene genome. To date, he has focused primarily on signals that regulate the gene for the α subunit of the acetylcholine receptor. Now, he and his collaborators are beginning to study what controls the activity of the genes that code for the other subunits—β, γ, and δ. ■

DEBORAH M. BARNES

Insect Viruses Invade Biotechnology

Baculoviruses, a hitherto obscure family of insect viruses, have become an important part of the biotechnology repertoire. More than 150 laboratories are currently using this viral system for the manufacture of proteins. Most notably, investigators at MicroGeneSys, Inc., in West Haven, Connecticut, recently used a specially designed baculovirus containing the envelope protein of the AIDS virus to produce the first AIDS vaccine approved for human trials in the United States (*Science*, 28 August, p. 973).

The ability to engineer the baculovirus has important applications in agriculture as well as medicine. Natural baculoviruses have been used since the early 1970s as biological insecticides. However, in areas with serious insect infestations, the viral infection process may be too slow. Lois K. Miller and co-workers at the University of Georgia in Athens and other investigators have been engineering baculoviruses to produce powerful insect neurotoxins, which may provide a more lethal weapon against such pests as the gypsy moth.



Baculoviruses. *A polyhedral crystal within an infected caterpillar cell. Intact baculoviruses appear as rods embedded in the polyhedrin matrix.* [*C. Y. Kawanishi, EPA, Research Triangle Park, NC*]

Baculoviruses are finding a niche in biotechnology because they can be engineered to express large amounts of proteins in a relatively short period of time. To do this, scientists have focused on the gene that encodes the viral polyhedrin protein, which surrounds virus particles within the infected cell. Gale Smith, now at MicroGeneSys, and Max Summers, of Texas A&M University and Texas Agricultural Experiment Station at College Station, spearheaded studies demonstrating that the regulatory signals that are so effective in producing polyhedrin can be diverted to the production of other proteins. When a butterfly or moth cell culture is infected with a recombinant baculovirus, the foreign protein can represent as much as 20 to 50% of the total protein made.

Like other viruses, the baculovirus uses its host's synthetic machinery to reproduce. The question of whether an insect system can turn out the same product as is made by the machinery of a human cell is of great concern if baculovirus proteins are to have medical applications. A protein that is not authentic might have harmful side effects if used therapeutically or as a vaccine. In many cases biological activity, the ability to induce an immune response, and enzymatic activity of the insect-produced proteins are very similar to those of the natural products. This similarity indicates that they are close, if not identical, to the authentic proteins. Phosphates are added to some newly made proteins in baculovirus systems. In addition, peptide sequences that direct proteins to their destinations in the cell can be close enough to the original that the proteins are delivered to the organelles where they would normally be found.

However, the addition of complex carbohydrate side chains to newly made proteins may not occur with fidelity in insect cells. This could be important for proteins containing sialic acid, fucose, or galactose. The issue will not be resolved until enough proteins produced in different insect cells have been sequenced and studied in a medically relevant setting.

Ongoing research on the applications of baculoviruses is also focused on optimizing the system. The amount of protein produced depends on such factors as the particular baculovirus and insect cell and the distance of the foreign gene from the polyhedrin control sequences. Commercially, it may be advantageous to grow baculoviruses directly in live caterpillars. According to David Bishop of the Natural Environment Research Council, Institute of Virology, Oxford, United Kingdom, one caterpillar can produce enough protein for as many as one million diagnostic tests. "It's easy to keep caterpillars," says Bishop. "Feed them leaves!"

Recently, Bishop and co-workers have developed a baculovirus that can express two added genes simultaneously. This virus proliferates easily in caterpillars and broadens the potential of this system for development of diagnostic tests (such as a single blood test that might detect exposure to hepatitis or the AIDS virus) and for the production of proteins containing two different subunits.

Other systems—principally yeast, *Escherichia coli*, *Aspergillus*, and mammalian cells—are available for large-scale production of proteins, although each one has its own problems. According to Summers, "We don't know enough yet about protein structure to predict which system will produce a particular recombinant protein that most closely resembles the original one." Which proteins will become part of the domain of the baculovirus system remains to be seen. ■ BARBARA R. JASNY

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