Cancer Among Metabolic Events

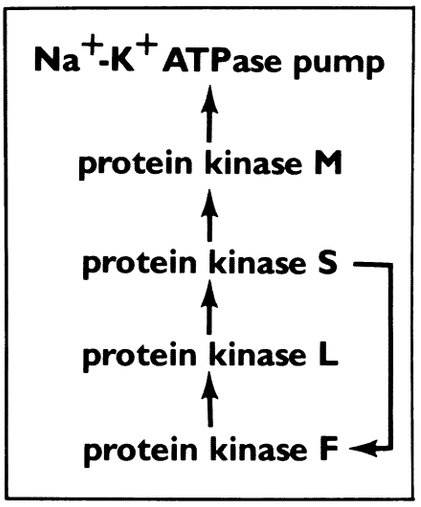
A single bad player in the orchestra of a cell's biochemical reactions can make the cell malignant. But from where in the ensemble does the discord arise? In research bringing together classical biochemistry and modern molecular biology, scientists are finding the first strong clues locating, among the metabolic pathways of a cell, events leading to the cell's transformation to malignancy.

At a seminar at the National Institutes of Health last week, Mark Spector of Cornell University described his recent research to an enthusiastic crowd, many members of which had heard of the still-unpublished results through the scientific grapevine. Although the seminar's arranger had deliberately chosen a relatively drab, or as he said "benign," title to go on the NIH events calendar, there was not even standing room at the talk given in the library of the Laboratory of Tumor Virus Genetics on the outskirts of the Bethesda campus. People sat on the chairs and table tops, crouched on the floor and perched on low bookcases, and still listeners crowded outside the doors.

Spector described one portion of the biochemical web now implicated in the transformation of some cells to a cancerous state. It is a cascade of reactions culminating in the transfer of a phosphate group to a protein complex that carries ions across the cell membrane. The cascade also adds phosphate groups to several other proteins, including one that is part of the cell's scaffolding, the cytoskeleton, so modification of these reactions can cause a variety of changes in a cell.

Efraim Racker and colleagues at Cornell were led to investigate these reactions by the observation that the ion pump, called the Na^+-K^+ ATPase, operates inefficiently in some tumor cells. They discovered that in a mouse tumor, but not in normal mouse brain, one subunit of the pump has a phosphate group attached. The addition of this phosphate turned out to be the finale of a cascade — four enzymes each catalyzing activation by phosphorylation of the next. The series resembles other cascades in cell metabolism that amplify biochemical signals, although Spector says the pattern is likely to be more complex. He already knows that one of the enzymes phosphorylates two of the others.

Phosphorylations are common means by which a cell controls biochemical reactions. But the ones Spector and Racker are investigating are not the garden variety. Traditionally a phosphate group is attached to the amino acid serine in a protein molecule. The active form of all four protein kinases in the cascade, however, has a phosphate group attached to a different amino acid, tyrosine.



A cascade of enzymes: Each activates the next. The cancer-causing genes of some animal viruses are closely related to members of this cascade.

This finding was provocative to cancer investigators. One set of enzymes was already known to attach phosphate groups to tyrosine. It is the proteins produced by the cancer-causing genes of some animal viruses called "retroviruses," and it is thought that these viral genes are pirated versions of cellular genes, important in development, that have been removed from normal control (SN: 3/7/81, p. 149).

Spector finds that in some cases the virus-encoded enzymes are very similar, if not identical, to the enzymes he and Racker have identified in the cascade. For example, one viral gene that transforms cells produces an enzyme closely related to protein kinase F; others produce an enzyme similar to each of the other three protein kinases. These results lead to the exciting hypothesis that uncontrolled production of any of these kinases can make a cell cancerous.

The cascade leading to phosphorylation of the Na^+-K^+ ATPase is not expected to be a universal mechanism for cell transformation, but it may set the style for others. Spector has recently examined 34 lines of animal cells growing in laboratory culture. Some, but not all, of the cells derived from tumors showed high levels of phosphate incorporation, and therefore may contain excess amounts of one of the cascade kinases.

Stanley Cohen at Vanderbilt University School of Medicine also has recently discovered a point in cellular metabolism where retroviruses could disrupt normal cell functions. He finds a similarity between the product of a cancer gene and an enzyme whose activity is stimulated when epidermal growth factor binds to its membrane receptor. Both enzymes phosphorylate tyrosines on at least one shared substrate. The enzymes don't seem to be identical, but, as Michael Bishop of the University of California at San Francisco says, "They are playing on the same keyboard."

"We really don't know what's going on yet," Spector cautions. But he and others are excited by the new possibilities. While chemicals and other viruses could have entirely different effects, it may be that they all cause cancer by creating discord, each in its own way, on a limited number of biochemical keyboards shared with normal developmental control. □

Progress against hepatitis B virus

When the hepatitis virus infects humans acutely, it causes debilitating disease and sometimes death. When it infects humans chronically, it seems to cause liver cancer. One way to fight this virus is with a vaccine, and researchers continue to report success in development of a vaccine that appears to be both safe and effective.

Jean Crosnier of Necker Hospital in Paris and his co-workers report in the Feb. 28 LANCET that they have found, in a double-blind, placebo-controlled trial, that a vaccine made from hepatitis B surface antigen was highly effective in protecting medical staff members at kidney dialysis centers against acute hepatitis B virus infection. Such staff members are at especially high risk of the disease. Of 318 subjects, 164 got three monthly injections of the vaccine and 154 got corresponding placebo injections. Whereas 12.3 percent of the placebo group came down with acute hepatitis B infection, only 3.6 percent of the vaccine-treated group did — a highly significant difference statistically. No hepatitis infection was observed after the 63rd day in vaccinated subjects. Success with a similar vaccine already has been reported (SN: 10/11/80, p. 231), and it now appears that vaccines made from inactivated hepatitis B antigens will eventually be used not only to protect persons at high risk of acute hepatitis B virus infection, but also to protect persons who are at high risk of becoming chronic carriers of hepatitis B virus and thus developing liver cancer.

Other scientists are working on techniques to make a hepatitis vaccine that is more abundant and less expensive than that now available, and also one that would be even more effective because it