Microvilli: A Major Difference Between Normal and Cancer Cells?

The surfaces of cancer cells differ from those of normal cells. Cancer cells do not adhere to each other as firmly as normal cells do and hence they behave as distinct entities (single units) when they invade tissues. Cancer cells also readily aggregate in the presence of concanavalin A (con A), whereas normal cells do not.

The effects of con A—which is a protein derived from jack beans—and similar substances have been seized on as a means of identifying differences between surfaces of normal and transformed, or tumor, cells. The effects of these substances on cell aggregation (agglutination) have been studied and described by many biologists in an effort to explain them. Now, Mark Willingham and Ira Pastan of the National Cancer Institute have advanced a new hypothesis directed to ascertain why and how con A agglutinates transformed, but not normal, cells. While not universally accepted, this new hypothesis is arousing a great deal of interest and debate among researchers.

The hypothesis of Willingham and Pastan ties together effects on cell agglutination of adenosine 3′,5′-monophosphate (cyclic AMP) and microvilli—which are hairlike appendages on the surfaces of some cells. Investigators including J. Sheppard of the University of Minnesota and those in Pastan's laboratory have reported that concentrations of cyclic AMP are low in transformed cells. Cells that have high intracellular concentrations of cyclic AMP behave normally, but those whose intracellular concentrations of cyclic AMP are low resemble cancer cells in their growth rates, shapes, adhesiveness to substratum, motilities, and abilities to bind together when exposed to con A. When cells with low cyclic AMP concentrations are prevented from degrading this nucleotide, the concentrations of cyclic AMP inside these cells increase, and, concurrently, the cells change their behavior and morphology and will no longer agglutinate in the presence of con A.

The presence of microvilli has also been reported to be correlated with cell transformation. Using scanning electron microscopy, Keith Porter and Virginia Fonte of the University of Colorado observed surfaces of a number of different kinds of tumor and normal cells. They found that the tumor cells had many more microvilli than the normal cells that were not dividing. Cells that were dividing resembled tumor cells in that they were covered with microvilli and agglutinated in the presence of con A. Although the function of microvilli is unknown, Porter and Fonte noted that when a cell is covered with microvilli it has a greater surface area than when its surface lacks microvilli and is relatively smooth. This increased surface area, especially in the form of microvilli, they suggested, might be related to an increased ability of cells to bind together in the presence of con A.

Putting together results relating to cyclic AMP and microvilli along with their recent observations of living cells, Willingham and Pastan propose that cyclic AMP controls the appearance of microvilli on cell surfaces. Further, they suggest that cells stick together more readily in the presence of con A when con A holds together microvilli of adjacent cells or when these microvilli aid in the entrapment of other cells.

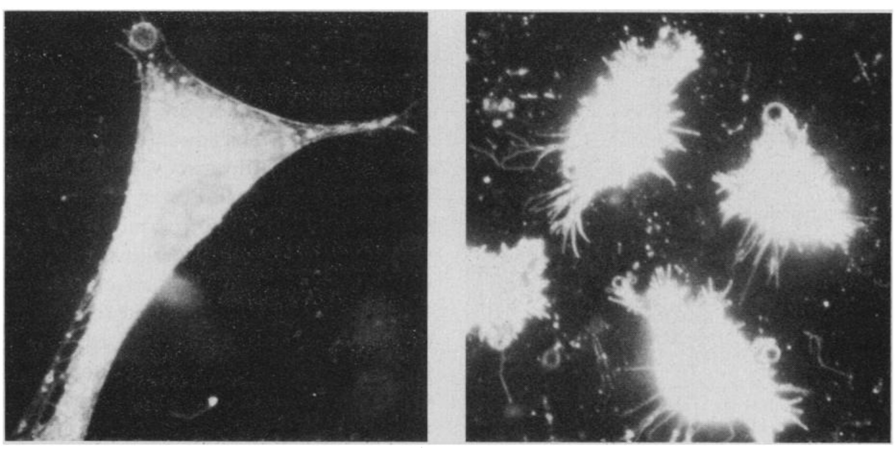

Fig. 1. Normal and transformed cells seen by dark-field microscopy. (Left) Normal 3T3-4 cell on glass (× 500). (Right) Transformed L929 cells on glass (× 500). [Source: Mark Willingham, National Cancer Institute]

Willingham noticed that microvilli, which cannot easily be seen with a phase-contrast microscope, can be seen with a dark-field microscope (Fig. 1). (Dark-field microscopy is based on reflection rather than refraction and permits slightly better resolution.) Willingham then examined 15 different kinds of transformed cells as well as their normal equivalents and found that all the transformed cells had microvilli, whereas normal cells did not.

The advantage of using dark-field microscopy to view microvilli, according to Willingham, is that it permits the observation of microvilli that would most likely remain undetected if the cells were observed by electron microscopy—which is the traditional means to view these structures. Willingham suggests that relatively few microvilli could be sufficient for agglutination. Some of these microvilli could collapse when the cells are prepared for electron microscopy, or they could simply be overlooked, particularly if the cells are sectioned for transmission electron microscopy. In fact, Willingham says he has seen microvilli on cells when he used a dark-field microscope, then has looked at the same cells with an electron microscope and has had difficulty finding the microvilli.

When Willingham and Pastan caused intracellular concentrations of cyclic AMP in transformed cells to increase, the microvilli regressed and the cells agglutinated poorly in the presence of con A. When they then caused the concentrations of cyclic AMP in those cells to decrease, the microvilli reappeared and the cells once again were agglutinable with con A. These results were reported at the ICN-UCLA Winter Conferences in Squaw Valley on 2 to 7 March 1975. The agglutinated cells could be seen, with an electron microscope, to be held together by interlocked microvilli.

Not all investigators believe that the hypothesis advanced by Willingham and Pastan entirely explains the agglutination of transformed cells by con A. Garth Nicolson of the Salk Institute for Biological Studies thinks that many kinds of transformed cells may not have significant numbers of microvilli. He disagrees with Willingham's assertion that microvilli could be missed if cells are observed by means of transmission electron microscopy or scanning electron microscopy.

Nicolson proposes that cell agglutination with con A (or other proteins that induce cell agglutination) is a complex process that involves many factors, some of which favor and some oppose, agglutination. The factors include the number and location (distance from the membrane surface) of con A receptor sites, electrostatic charges on cell surfaces, structures such as microvilli, cell surface deformability, the mobility of con A receptors in cell membranes, and the control of that mobility by elements in the cytoplasm that are in turn controlled by cyclic AMP. Nicolson does not believe that cell agglutination can be explained by any single property of cell surfaces, although in certain systems some properties may be more important than others. He says that a given group of cells will agglutinate if the factors favoring this process outweigh the factors that oppose it.

Since dark-field microscopy has not been used previously to observe microvilli, many investigators are waiting to support the hypothesis of Willingham and Pastan until more cells have been observed in this way and until cells have been observed under a wide variety of experimental conditions. Others are enthusiastic about the hypothesis because of its simplicity and apparent generality. Still others agree with Nicolson's criticisms of it. Whether or not Willingham and Pastan turn out to be right, it now seems likely that microvilli will play a prominent role in future investigations of differences between normal and transformed cells.—GINA BARI KOLATA

Energy Conservation: Better Living through Thermodynamics

Modern fossil fuel generating plants have an efficiency of about 40 percent, typical household furnaces have an efficiency of 60 percent, and electric hot water heaters have an efficiency of about 75 percent.

Such a comparison seems to imply that 100 percent efficiency is the best theoretically possible, and that hot water heaters are more nearly perfect than generating plants. But closer study of the laws of physics shows that both of these implications are false. For fossil fuel generating plants the maximum theoretical efficiency is less than 100 percent, while for home heating devices it is considerably greater than 100 percent, just as it is for home cooling devices. The quantity that would otherwise be called efficiency for air-conditioners is so embarrassingly high that it is renamed the "coefficient of performance."

A number of studies of the energy economy have pointed out that the calorie content of fuel is not a very good index of wastefulness, since energy is not actually consumed (according to the first law of thermodynamics), but is rendered useless by an increase of entropy (according to the second law). A more important quantity is the ability of energy to do work, which is a more subtle thermodynamic quantity related to the concept of "free energy" introduced by J. W. Gibbs in 1878, and known to physicists and engineers as "available work." The second law of thermodynamics virtually guarantees that a quantity of high-temperature energy can do more work than an equal amount of low-temperature energy.

The shortcomings of the usual definition of energy efficiency are particularly apparent for tasks in which fossil fuels are used to produce low-temperature heat. Since fossil fuels burn at very high flame temperatures—up to 4000°F (2210°C)—the available work produced by fossil fuels is largely wasted when it is used for hot water heating, space heating, or even industrial steam production, since these are relatively low-temperature processes. For such purposes, the fuel could often be better used to raise the temperature of heat pumped in from another source rather than to produce heat directly by burning. Alternatively, the fuel could be used to do additional work, such as generating electricity, in the course of producing a low-temperature output.

Summer studies by the American Physical Society (APS) and the International Federation of Institutes of Advanced Study in 1974 have recommended that available work should be the measure of efficient energy utilization used for assessing wastefulness in various sectors of a national energy economy. The APS study,* for which the principal investigators were Robert Socolow at Princeton University and Marc Ross at the University of Michigan, proceeded further to recommend an improved definition of energy efficiency based on the minimum amount of available work needed for a task, and named it the "second-law efficiency." The more familiar measure would then be called the "first-law efficiency," and a comparison of the two measures estimated by the APS study is given in Table 1.

Table 1. Comparison of energy efficiencies derived from the first and second laws of thermodynamics. The familiar or first-law efficiency does not reflect the minimum theoretical energy needed for the task and so may be misleadingly high, especially for low-temperature heating requirements. [Source: "Efficient use of energy: A physics perspective," a report of an American Physical Society summer study of 1974]

Use	Estimated first-law efficiency (%)	Estimated second-law efficiency (%)
Space heating		
Furnace	60	6
Heat pump*	270†	9
Water heating		
Electric	75†	1–2
Gas	50	3
Air-conditioning	200†	5
Refrigeration		4
Industrial		
Process steam		~25
Direct heat		~30
Electric drive		30
Transportation		10

*Heat pump efficiency is here calculated for an indoor temperature of 110°F (before distribution) and an outdoor temperature of 40°F. Heat pumps are much less efficient in colder weather. †The first-law efficiency is smaller by a factor of 3 if stated in terms of the electric power plant fuel. Second-law efficiency must be based on power plant fuel.

The second-law efficiencies of space heating, water heating, air-conditioning, and refrigeration are all less than 6 percent. In other words, each of these processes requires almost 20 times as much as the minimum energy to do the task consistent with the laws of physics. Of course, any practical device will fall short of idealized performance, but "it is within reach of the present technology to come considerably closer to the ideal," according to the APS report. For relatively high-temperature processes, such as industrial direct heat, there is not so much difference between the first- and second-law efficiencies. However, low- and moderate-temperature processes account for 45 percent of the total U.S. energy usage.

Perhaps the first example of a government order that incorporated the concept of second-law efficiency into a discussion of efficient fuel utilization was a recent action by the Federal Power Commission (FPC). In a request for permission to use offshore gas to fuel refineries in southern Louisiana, Exxon, Cities Service, and Continental oil companies argued for the energy efficiency of the plan by comparing the fuel value of the refined oil to the energy value of the crude oil feedstock plus the gas needed for refining. One witness at

*Summaries are available from Kurt Riegel, Federal Energy Administration, Room 5320, Washington, D.C. 20044.