departments. It has been common practice for employees who proved incompetent to be shoved into the personnel office where they were supposed to be relatively harmless. But as selection procedures have become more sophisticated the importance of well-trained personnel officers has become obvious.

Adopting employment procedures that are both professionally and legally sound is difficult and expensive, and some employers may deeply resent that, in addition to the goal of making a profit, they must also actively incorporate the goal of social justice (just as they are being forced to take responsibility for environmental clean up). But society must pay for its discards in one way or another, as it must pay for all the corporate inefficiency and personal misery that results from haphazard, biased, and inappropriate employee selection and placement. What now seems the most difficult and expensive route may prove the least costly.—CONSTANCE HOLDEN

RESEARCH NEWS

Cell Surface Protein: No Simple Cancer Mechanisms

Whether a cell is normal or cancerous could hinge on the presence or absence of a few key molecules. Tumor viruses or chemical carcinogens could convert normal cells to transformed cells (that is, tumor cells) by preventing or altering the expression of one or several genes whose products are necessary for normal cellular metabolism. Since this explanation of transformation has long been considered plausible, cell biologists have spent years looking for proteins that are present (or absent) in all normal cells, regardless of the kind of cell, and absent (or present) in all transformed cells, regardless of the means of transformation.

About one and a half years ago, investigators at six different laboratories, using four different experimental techniques, independently discovered that one gene product—a large cell surface protein—is lost when cells are transformed. This large external transformation sensitive (LETS) protein has a molecular weight of 250,000, contains the sugar galactose, and is found on normal cells from a wide variety of species, including human beings, rats, and chickens. Moreover, some investigators found that when normal cells are exposed to enzymes that strip off their LETS proteins, they can lose control of their growth and biochemically and morphologically resemble transformed cells.

The loss of a cell surface protein could conceivably be a crucial event in cell transformation. Transformation involves changes in growth rate, morphology, adhesion, metabolism, and migration of cells. A cell surface protein could affect the expression of any or all of these things. For example, it could affect growth control and adhesive properties of cells by altering the membrane structure. Removal of such a protein could be one step in a chain of events that occur during transformation or it could be the primary event in transformation. However, recent studies of the LETS protein indicate that unraveling its function in transformation may not be as straightforward a matter as was originally hoped. The protein is now believed to be involved in cell adhesion. But there is some question as to whether its absence is necessary for other aspects of transformation.

Three groups of investigators who discovered the LETS protein used the enzyme lactoperoxidase to attach radioactive iodine to this protein and so observe its presence on normal cells and absence on transformed cells. Other investigators labeled the galactose portion of LETS with a different enzyme—a galactose oxidase—to monitor the presence of this protein. A third way in which LETS was discovered was with immunochemical methods. A fourth method was employed by a group of investigators who measured changes in membrane polypeptides of transformed cells.

Kenneth Yamada, now at the National Cancer Institute, and James Weston of the University of Oregon developed a method to isolate the LETS protein of chick embryo fibroblasts and demonstrated that the isolated protein is capable of reattaching to cells from which it had been removed. This method provides a way of studying the function of LETS by observing the consequences of its addition to cells.

Results obtained with the purified LETS protein and indicating that it may play a role in cell adhesion were recently reported by Yamada, Susan Yamada, and Ira Pastan of the National Cancer Institute. Although this role is not firmly demonstrated, the experiments of Yamada and his associates are of interest because they provide the first direct evidence of a biological function for the LETS protein.

One test of whether the LETS protein is involved in cell adhesion is based on the observation that certain cell adhesion proteins cause red blood cells to agglutinate. Steven Rosen of the University of California at San Diego demonstrated this for a protein that presumably causes slime mold cells to adhere. Yamada and his colleagues report that the LETS protein, isolated from chick embryo cells, agglutinates red blood cells and thus behaves like the slime mold protein.

The ability of the purified LETS protein to agglutinate red blood cells vanishes in the presence of antibodies to LETS, chelating agents such as EDTA, and proteases (enzymes that degrade proteins) such as trypsin. Chelating agents and trypsin are routinely used to dissociate cells. In addition to this evidence that the LETS protein may function in cell adhesion, Yamada reports results indicating that LETS can cause other kinds of cells to adhere. When he added purified LETS protein from chick embryo cells to dissociated chick embryo cells or to transformed rat kidney cells, the cells aggregated (Fig. 1).

If the LETS protein plays a role in cell adhesion this could help explain why transformed cells frequently show decreased adhesiveness. However, it remains possible that this protein may also be necessary for the expression of other traits that distinguish normal from transformed cells. Richard Hynes, now at the Massachusetts Institute of Technology, and Jacqueline Bye of the Imperial Cancer Research Fund and, independently, Carl Gahmberg and Sen-Itiroh Hakomori of the University of Washington, report that the presence of the LETS protein on the surfaces of normal hamster cells varies with the stages of cell growth in a way that might be expected if LETS were involved in growth control. Hynes and Bye detected the LETS protein by attaching radioactive iodine to one of its amino acids, whereas Gahmberg and Hakomori labeled the LETS protein with radioactive borohydride. Absence of detectable LETS protein could mean that the protein was missing from cells or that it was inaccessible to reagents that react with the surfaces of cells.

Hynes and Bye, as well as Gahmberg and Hakomori, find that the amount of iodinated LETS protein on normal hamster fibroblasts is greatest when the cells are resting rather than growing. The amount of LETS protein on growing cells decreases as the cells approach the stage of the cell cycle at which they divide. At mitosis, the cells have little or no detectable LETS protein. Since mitotic cells re-

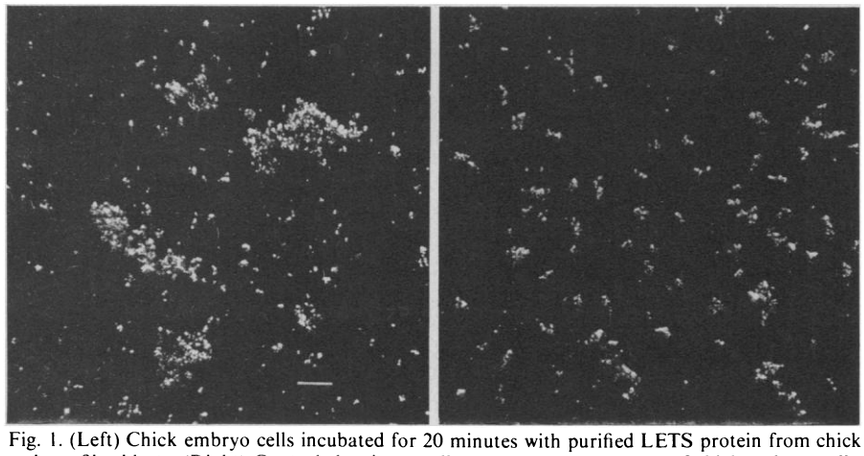

Fig. 1. (Left) Chick embryo cells incubated for 20 minutes with purified LETS protein from chick embryo fibroblasts. (Right) Control showing small spontaneous aggregates of chick embryo cells. [Source: Kenneth Yamada, National Cancer Institute]

semble transformed cells according to a number of biochemical and morphological criteria, it might be expected that if the LETS protein is involved in growth control, it would be absent from the surfaces of mitotic cells.

Several investigators have suggested that transformed cells may lack the LETS protein because the cells excrete proteases that destroy it. It is known that the LETS protein is easily destroyed by proteases and that transformed cells excrete proteases, whereas normal cells do not. Moreover, when normal cells are mixed with transformed cells or when normal cells are exposed to any of a wide variety of proteases, the normal cells lose their LETS protein.

One particular protease, plasmin, has been frequently implicated in transformation (*Science*, 29 March 1974). Edward Reich and his colleagues at Rockefeller University found that transformed cells secrete a substance that converts an inactive form of serum plasmin into an active protease. Reich showed that plasmin is involved in the expression of a number of characteristics of transformed cells, such as migration into a wound in the absence of serum, growth in agar, and a number of morphological traits.

Hynes and his associates undertook an investigation of the role of proteases—and, in particular, plasmin—in transformation. First, they sought to determine whether plasmin causes the removal of the LETS protein from normal cells when they are mixed with transformed cells. They found that, although plasmin can destroy the LETS protein on cell surfaces, its destruction is not necessary for the removal of LETS. Normal cells mixed with transformed cells in the absence of serum, where plasmin is found, or in serum depleted of plasmin still lose their LETS protein.

Although plasmin is not necessary for the removal of the LETS protein from normal cells when they are mixed with transformed cells, some other protease may be. However, after several experiments, Hynes and his associates ruled this less likely, although not impossible. They were unable to effect the removal of LETS from normal cells when they added the mediums from transformed cells to the normal cells. And they could not prevent the removal of LETS from normal cells mixed with transformed cells when they added a number of protease inhibitors, including some effective against plasmin, to the cells.

Hynes and his associates reasoned that it may be easier to prevent transformation with protease inhibitors than to reverse it once it had occurred. Accordingly, they studied the effects of protease inhibitors on the transformation of chick cells by a temperature-sensitive tumor virus. This particular tumor virus causes transformation when infected cells are grown at 36°C but not when they are grown at 41°C. Hynes and his colleagues report that, with one exception, the protease inhibitors they tested did not prevent transformation. They added these inhibitors to infected chick cells growing at 41°C and then lowered the temperature to 36°C. The one exception, a protease inhibitor called tosylphenylalanine chloromethyl ketone, is also an inhibitor of protein synthesis, so the means whereby it prevents transformation is unclear.

Although most experiments designed to probe the role of the LETS protein lead to results that do not rule out the hypothesis that it plays a primary role in transformation, some investigators are beginning to doubt that this hypothesis is correct. Nelson Teng and Lam Bo Chen of the Massachusetts Institute of Technology, for example, report evidence that removal of the LETS protein may be sufficient, but not necessary, for one aspect of transformation—the loss of growth control.

Teng and Chen discovered that one protease—thrombin—causes resting chick fibroblasts to divide without removing the LETS protein from their surfaces. Although the possibility remains that thrombin damages the LETS protein, Teng and Chen find that the LETS protein from thrombin treated cells still has a molecular weight of 250,000 when measured in SDS gels. Since thrombin degrades proteins, it should affect the molecular weight of the LETS protein if it attacks it.

Other possibilities are that thrombin alters some other protein that is necessary for the action of the LETS protein or that LETS is not necessary for growth control but some other thrombin-sensitive protein is. Chen favors this latter hypothesis and notes that he and Teng have discovered a new protein of molecular weight 200,000, whose removal may be necessary for cell proliferation. This new protein is removed from the surfaces of chick cells by thrombin and also by trypsin. Moreover, the new protein is absent from chick cells transformed by a tumor virus.

Yamada believes, along with Teng and Chen, that it is becoming less and less likely that the LETS protein is the key protein whose absence causes cell transformation. He points out that, if the absence of the LETS protein caused cell transformation, it should be the first thing to go when cells become transformed. However, both he and Hynes and others find that there is a lag of several hours between the time when cells infected with a temperature-sensitive tumor virus are shifted to a lower temperature, at which point transformation begins to be expressed, and the time that the LETS protein disappears from the surfaces of those cells. Hynes finds that there is a lag between the time that resting cells are stimulated to grow by the addition of fresh serum and the time that the LETS protein disappears from their surfaces.

In order to settle the issue of whether the removal of LETS causes transformation, it will be necessary to add purified LETS protein to transformed cells and see if the cells revert to normal. Then, if the cells revert to normal, it will be necessary to see if the reversion can be blocked by antibodies to LETS. Both Hynes and Yamada have succeeded in extracting and purifying large quantities of LETS from chick cells and in obtaining antibodies to this purified protein. Both plan to add purified LETS protein to transformed cells.

Whether LETS protein has a role in transformation still remains to be determined. However, it now seems unlikely that studies of this protein can provide a simple answer to the question of how transformation occurs.

—GINA BARI KOLATA