Cancer Cells: More Needles in the Haystack

A surprising and intriguing finding has just boosted the harvest of fine biochemical differences between normal and cancerous cells. While one group of researchers is focusing on the primary event — identification of cell-transforming proteins (SN: 11/13/82, p. 316) — other scientists are looking one step further down the line. Because the dramatic differences observed between normal and cancerous cells are unlikely to arise directly from a single agent, investigators are seeking additional genes within a cell that may be activated or repressed by the initial cancer-causing protein. One group now reports an immune system gene — containing an element that may be a developmental tag — is activated in cancerous cells.

The search for such increases and decreases in gene activity has often been likened to the proverbial search for a needle in a haystack. In the vast majority of its detailed operations, a cancerous cell resembles a normal one. Scientists estimate that in cells made cancerous by a virus called SV40, for example, 97 percent of the messages (messenger RNA molecules) reaching the protein-making machinery are also found in normal cells.

Now scientists at the Imperial College of Science and Technology in London report a method for finding "needles" by removing the haystack. They use DNA from normal cells to bind DNA representing the cancer-cell messages shared with normal cells, leaving free the messages specific to the cancer cells.

This method can identify genes that produce as little as 0.01 percent of the total amount of messenger molecules present in a cell, Peter J. Rigby and colleagues say. They found, by this process, 42 messenger RNA molecules present in mouse cells transformed by SV40 virus but not present in normal cells. At least one of these, which they call pAG64, represents a gene that appears to be activated in a wide range of mouse cancers, representing different cell-transforming proteins.

"The complete nucleotide sequence of pAG64 has been determined," Paul M. Brickell, Rigby and colleagues report in the Dec. 22/29 NATURE. "To our considerable surprise," they write, comparison of the pAG64 sequence with previously known nucleotide sequences indicated that it represents a gene of the group called the major histocompatibility complex, which allows the immune system to distinguish self from non-self.

More detailed analysis led the scientists to conclude that this gene is not of the set responsible for proteins on the surface of most cells. But the gene belongs to a neighboring, less well-characterized group called the Qa/Tla region. These genes make proteins found on the surface of the blood cells — lymphocytes and thymocytes. Identification of the gene represented by pAG64 may lead to a better understanding of the operation and function of this part of the immune system.

Another exciting aspect of the newly found gene may influence research on how an organism develops from an embryo to an adult. Rigby finds that the new gene contains an element that may serve as a tag for expression during normal embryonic development. This element, a length of DNA, is present thousands of times throughout a mouse's set of chromosomes. Two other genes that Rigby and colleagues have identified as active only in cancerous cells have the same sequence. Rigby and colleagues also find this repetitive sequence in a number of genes active during a specific stage of mouse embryonic development.

Identification of this repetitive sequence supports the idea that elements present in many widely dispersed copies may flank genes that are expressed coordinately and may be important in their regulation during an organism's development. The primary cancer-causing proteins or a regulator of normal development may bind to the repetitive sequence and influence the adjacent gene's activity.

—J. A. Miller

Genes and cancer: This time for diagnosis

Cancerous cells can often be categorized by appearance or biochemistry: how they look under a light microscope, how they react in the presence of certain chemicals. But sometimes they guard their identity more closely, confusing physicians and confounding treatment.

Government researchers have found a way to identify certain difficult-to-distinguish cases of a cancer called B-cell lymphoma by going to the heart of the matter — the genes of the cells in question. Andrew Arnold and colleagues at the National Cancer Institute in Bethesda, Md., have used the method in 10 cases where standard diagnostic methods failed. The method, they hope, will eventually prove useful with other types of cancers as well.

B cells are members of the immune system that circulate in the blood and lymph fluid. Each B-cell membrane is dotted with a specific protein molecule called an immunoglobulin, which acts as a lookout for a particular foreign substance. To produce that unique immunoglobulin, certain B-cell genes rearrange themselves on their chromosomes.

When the provoker is encountered, the B cell begins rapidly dividing, producing an army of identical cells that make intruder-binding immunoglobulin. In a B-cell lymphoma, one of these B cells reproduces itself uncontrollably.

Each immunoglobulin, and thus each B cell before dividing, is unique. The B cells can be identified by their immunoglobulins, and most B-cell lymphomas can be identified by characteristic immunoglobulins or other biochemical markers. But sometimes the cancerous B cells don't have immunoglobulins, or the other markers, on the cell surface, which is why Arnold and his colleagues decided to look a bit deeper — to the rearranged DNA — to categorize the cells.

He and his colleagues extracted the DNA from tumor-associated cells and broke the molecules into pieces using enzymes that slice DNA at specific places. Normal B cells — each with a unique rearrangement — yield a smear of different-sized pieces from the different immunoglobulin genes. A disproportionate number of pieces of one size — one chromosome fragment — indicates that one cell has parented a disproportionate number of progeny.

The technique has been used before on leukemic cells, Arnold notes. "What's a little different about lymphomas is that the tissue sample you get in your biopsy very frequently contains only a small minority of cancerous cells and you can have surrounding that cancer a large mass of normal cells," he says.

Typical carcinomas — at least the 11 the group checked for comparison — do not show rearrangement in the areas coding for the immunoglobulin genes, the researchers report in the Dec. 29 NEW ENGLAND JOURNAL OF MEDICINE.

"The work has implications beyond the realm of lymphoid tumors," says Arnold. "DNA alterations occur in many other types of cancer, and it is only a matter of time before genes involved in the other types of cancer will be available. At that point the methods we have used will be applicable to more common tumors like lung and breast cancer and may improve diagnostic capabilities as well as the knowledge of how genetic changes can cause cancer."

— J. Silberner