# Genetic Roadblocks

## The body may not always resist cancer, but it does have built-in barricades to slow the spread

By LAURA BEIL

At first, the idea seems almost *too* good: a gene that keeps cancerous cells from traveling through blood and lymphatic vessels, ambushing other parts of the body like highway bandits. If an inherited code could prevent metastasis — the point at which tumor cells break free and spark other tumors — a serious condition might be kept from becoming a deadly one.

Gene or no gene, the body has some built-in roadblocks slowing the spread of cancer. Malignant cells must first push past the barrier of connective tissue between cell layers, then weather the body's immune attack, then successfully colonize new sites. For this, they pack an arsenal of enzymes, but as is the case with most of the biochemical dynamics of cancer, research still falls short of explaining why some tumors migrate while others lie silently.

Genetics makes the difference, says a group of researchers at the National Cancer Institute (NCI). They believe that somewhere among the twists and tangles of human chromosomes lies a formula constraining at least some types of cancer. One of the candidates currently penciled in under the heading of "cancer suppressor genes" is thought not to prevent cancer but to block metastasis. The gene is labeled, unromantically, NM23.

Whether a metastasis suppressor is synonymous with a cancer suppressor depends on whether a person views cancer in strictly the cellular sense or as a complicated disease, says Webster Cavenee, director of Ludwig Institute for Cancer Research in Montreal, Quebec. As an illness, cancer has two stages: the initial tumor development and that tumor's invasion into other parts of the body. Cancer rarely kills until it spreads.

"I think that anything that suppresses any part of the process can be called a cancer suppressor gene," Cavenee says. "Metastasis in particular has been a tough one to get hold of."

But a cancer suppressor gene of any sort must jump through three hoops, and so far none has, says NCI's Patricia Steeg, discoverer of NM23. First, the gene must be active in normal cells. Second, it must be turned off in cancerous ones. And third, it must be able to turn cancerous cells into normal ones (or metastatic cells into nonmetastatic ones).

Several genes have passed the first test: They code for proteins in normal cells. The second test requires that a loss of expression — an inactivitation of the gene through either a chromosomal deletion or DNA mutation — lead to a cancerous cell. Human cancers of the kidney, muscle, liver, colon and bone are among those whose cells have gaps in a certain portion of the chromosome. This does not pinpoint a cancer suppressor gene, but only identifies a region where one might have been.

In the case of NM23, loss of the gene is linked to a cancer cell becoming metastatic. The only other sequenced and cloned suppressor-gene contender keeps cancer from the eye's retina cells as long as the gene remains intact. Resting on the long arm of chromosome 13, it is called the retinoblastoma gene and has been known to researchers for several years (SN: 1/5/85, p.10).

At her laboratory, Steeg found NM23 in three kinds of rat and mouse tumors with low metastatic potential before focusing her experiments on human breast cancer cells last year. Currently, the decision of how best to treat breast cancer hinges on the potential of the cancer to spread into lymph nodes and beyond (SN: 5/14/88, p.314). If physicians could accurately predict which cancers would metastasize, women for whom chemotherapy proved unnecessary could be spared the treatment's harsh side effects.

"Diagnosis makes a difference in treatment, and right now there's a problem predicting who will metastasize," Steeg says. Ideally, the presence or absence of the NM23 gene could help physicians gauge the metastatic potential of the cancer.

Steeg and her colleagues searched for the gene in tumor cells from 17 breast cancer patients by testing for its corresponding messenger RNA (mRNA), a unique flag for the gene. "The NM23 mRNA levels were found to decline in tumors from women with many involved lymph nodes, an indicator of high metastatic potential," she says.

"More importantly," she continues, "30 percent of the patients with no or few involved lymph nodes also had primary tumors with low NM23 mRNA levels." The sample, however, was small, and the results remain inconclusive. The researchers are now following those patients to see whose cancers actually metastasize.

To meet the third criterion, a suspected cancer suppressor gene should, when incorporated into cancer cells, make the cells normal. But Steeg says it will take years to get data on this level, as the whole process of proving cause and effect — which involves boosting the expression of the gene — becomes tricky. She and her colleagues have begun injecting mice with tumor cells that have incorporated the NM23 gene. If the gene does what she thinks, those cells should not be metastatic. "But at this point all we have is a correlation [from past investigations]," she emphasizes.

Lance Liotta, director of the NCI's Laboratory of Pathology, observes that strong inferences can be made from correlations, but the more important data for NM23 and other cancer suppressors are still on the horizon. He says flatly, "The real proof that some gene is a suppressor is to take that gene and put it into a cancer cell and see if it suppresses it."

Since most cancer suppressor genes still elude modern science, no one is quite sure how they work or how specialized they might be. "These genes are probably not going to be so specific that there is one gene to one cancer, but not so broad as to be one gene to all cancers," remarks Cavenee, who helped isolate the retinoblastoma gene. Most recently, in the July 15 SCIENCE, scientists reported a link between a damaged retinoblastoma gene and lung cancer in smokers, suggesting that cigarette smoke may harm the gene and unleash malignancy in the lungs.

If scientists do find suppressor genes for cancer formation and metastasis — and most researchers in the field say they will, eventually — the next step will be streamlining a test to predict what lies in wait for some patients. The test would actually look for the protein the gene codes for, not the gene itself. But up to now, even NM23's protein has remained evasive, and the aggressiveness of cancer remains, as Cavenee puts it, "almost mystical." □