Genetic diversity in tumor cells may muddle therapy

Conventional cancer wisdom traces the growth of a raging tumor to a single cell gone awry: One or two missteps in the genetic code of one cell leads to uncontrolled production of daughter cells, each genetically identical to the first. The slight environmental differences that shape each cell can prompt larger differences in growth rate, or resistance to chemotherapy that confound physicians (SN: 2/27/82, p. 135). But scientists have assumed that at least the bare bones genetics of each cell in a given tumor are the same.

But surprising findings of two genetically distinct cell types in tumors of four patients at Stanford University School of Medicine challenge that long-held belief, and suggest that diagnosis and treatment of some cancers may be even more complex than first thought. The Stanford scientists say their findings may pose a special roadblock to the therapeutic use of monoclonal antibodies, proteins designed to specifically seek out and destroy malignant cells while sparing healthy tissue.

Jeffrey Sklar and five co-workers studied 20 patients with B-cell lymphoma, a fairly common cancer of antibody-producing immune cells. (About 20,000 to 25,000 new cases of the cancer are detected in the United States each year.) A battery of tests on samples of several tumor sites in each patient predictably showed most cancerous nodes to be homogenous overgrowths of one type of cell. But 20 percent of the patients, described in the July 5 NEW ENGLAND JOURNAL OF MEDICINE, possessed a "biclonal" tumor, composed of two genetically distinct cell lines.

The most likely explanation for the finding, Sklar says, is that the two clones share a common ancestor cell. According to the theory, which is still being tested, one primitive cell in the bone marrow somehow acquired a genetic message for malignancy which it passed on to its descendants. Several cell generations later, the cancerous message was activated, producing the rapid, unchecked cell growth known as a B-cell lymphoma.

At a basic research level, the findings show that "our concept of B-cell lymphoma has been faulty," Sklar told SCIENCE NEWS. The work indicates that the primary malignant cell can occur much earlier in B-cell development than was previously thought, he says.

At a clinical level, the findings further complicate the use of monoclonal antibodies as "magic bullets" to fight tumors. What Sklar calls "microheterogeneity," a mixed bag of metabolic characteristics that can overlay the same genetic backbone in neighboring tumor cells, has been recognized as a problem in cancer therapy for several years, he says. But his results supply evidence for a more fundamental kind of tumor heterogeneity that arises because two cells are genetically distinct. Because the antibody treatments are designed to recognize only one type of cell, a second group of cells in a biclonal tumor might be unaffected by therapy.

Diagnosis may also become more difficult, he says, because physicians will no longer be able to rule out cancer when they find more than one type of cell in a biopsy sample. A mix of several antibodies might address the treatment problem, he says, but would require multiple biopsies from several sites on the patient's body, throughout the course of disease, to make certain all types of cancerous cells are detected.

One solution to the problem might be to somehow reduce the specificity of the antibody only slightly, and develop antibodies that react with more than one target. Unfortunately, each reduction in specificity increases the chances that some healthy cells will be killed as well. "You're constantly trying to balance specificity with generality," Sklar says.

—D. Franklin

Sex differences in the brain: Coming out of the closet

There's a bit of tissue deep within each rat brain that plays a crucial role in whether that rat behaves like a male or female. Two recent studies based on transplants of the area — known as the sexually dimorphic nuclei of the medial preoptic area (MPOA)—offer new clues to the mystery of just what determines sex-related behavioral differences.

Roger Gorski and colleagues from the University of California at Los Angeles transplanted tissue from young male rats to their female littermates, which caused certain male mating behaviors in the females. The result, Gorski said last week at the 7th International Congress of Endocrinology in Quebec City, "indicates that the brain tissue has been incorporated functionally."

"I'm still very surprised that we can modify behavior," he says. "We believe that our work involves actual connections but we have not proven it yet."

Ronald Hammer and colleagues at the National Institute of Mental Health in Bethesda, Md. have also transplanted tissue of the MPOA, which Hammer considers to be "the brain's anatomical counterpart to the gonads." They find that opiate receptors on the membranes of nerve cells in the area show definite male or female patterns.

Normally, female rats during half their estrus cycle have a high concentration of opiate receptors in and around the sexually dimorphic nucleus; females in the other half of their cycle, and males at all times, have a lower concentration. When Hammer transplanted male brain tissue into females, that tissue had a malelike receptor pattern. These results "may explain why hose females show enhanced male behavior" after the transplantation, he says.

Behavioral changes that Gorski and others elicited years ago by manipulating rats' hormones during the first few days of life, before the rats became sexually differentiated, are mirrored by changes in the density of opiate receptors on the brain cells Hammer has found. "The nice thing is that what's happening with the opiate system is exactly the same as what happens with the [sexually dimorphic] nucleus," he says.

Because all rats have the same concentration of the receptors just after birth, before their sexual differentiation has occurred, it means that "opiate receptors — and probably opiates themselves — play a role in sexual differentiation and later on in sexual behavior," Hammer says.

But is it cause or effect? Since opiates such as morphine can inhibit reproductive behavior, Hammer believes it is cause. Though asexually dimorphic area in humans has not been identified, Hammer says that disturbing the opiate system — such as by use of narcotics — could cause reproductive problems.

In both cases, the transplanted tissue evidently made complex interconnections in its new home. Other laboratories have had success in getting transplanted tissue to establish itself and function — adult diabetic rats were cured with healthy fetal brain tissue (SN: 12/20 & 27/80, p. 389), transplanted hypothalamic tissue has shown activity (SN: 8/14/82, p. 101), and researchers working with rats have been successful in getting transplanted brain tissue to supply the missing chemical that causes Parkinson's disease (SN: 11/20/82, p. 325). But in the sexual behavior work, Hammer notes, the effort has not been to get transplanted tissue to supply a specific needed chemical but to elicit a complex behavior controlled by as yet poorly understood physical and chemical factors. Even without knowing the exact chemicals involved or the precise anatomical connections, "we still got the motor output," he observes.

—J. Silberner