Chromosomal Fragility

Can unstable segments of DNA explain some cancers?

By NATHAN SEPPA

Fragile sites, chromosome regions that are prone to break apart or suffer mutations, appear to be weak links in the chain of events that guides development from embryo to adult. Scientists report growing evidence of breaks at these fragile locations in cancer cells—hinting at a connection between these sites and the disease.

Their findings raise a chicken-and-egg question: Does cancer destabilize these fragile sites, or does prior genetic damage at these sites foster cancer?

"We just don't know which is the case," says geneticist Thomas W. Glover of the University of Michigan in Ann Arbor.

Several research groups are now testing the second possibility and getting provocative results. Indeed, one fragile site under suspicion—a long string of DNA on human chromosome 3 called FRA3B—is often disrupted in breast cancer, researchers reported last month in Denver at a meeting of the American Society of Human Genetics. Other recent work has detected fragile site disruptions in pancreas, stomach, lung, esophagus, and kidney cancers. Scientists at the meeting also presented evidence for a mechanism—incomplete DNA replication—that may underlie these sites' fragility.

Scientists have found roughly 100 fragile sites to date. Mental retardation has been shown to result from relatively rare damage at one well-known site, called fragile X. At 84 of the sites, disruptions are more common, and FRA3B is often damaged, says Michelle M. LeBeau, a cancer geneticist at the University of Chicago.

This site is part of a large gene, called *FHIT*, that was identified 2 years ago by molecular geneticist Kay Huebner and her colleagues at the Kimmel Cancer Center at Jefferson Medical College in Philadelphia. Since then, the group has been working to ascertain whether *FHIT's* fragility plays a role in the start or progression of cancer.

Based on a collaboration with researchers led by Sigurdur Ingvarsson of the University Hospital of Iceland in Reykjavik, Huebner reported preliminary findings at the conference from a study of 37 women with hereditary breast cancer. Tumor cells in 31 of these women showed variously reduced concentrations of the protein that *FHIT* encodes, Huebner says.

The women all had a defective *BRCA2* gene that predisposed them to cancer. The high frequency of FHIT deficiency in the cancer cells could indicate that women with a missing or altered *BRCA2* gene "are unable to properly repair double-strand breaks" in DNA that occur in the FRA3B region of *FHIT* (SN: 6/21/97, p. 386).

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Among 109 other women who had breast tumors but who weren't carriers of the *BRCA2* mutation, the researchers found that about 30 percent had reduced concentrations of the FHIT protein.

In an ongoing study of 50 patients with stomach cancer, Huebner reports that 27 were missing the FHIT protein and those patients had shorter average survival times.

Although it's a large gene, *FHIT* encodes a small protein whose function is still unknown. Huebner speculates that this protein is a cancer suppressor.

"Looking for damage in *FHIT* might have diagnostic and prognostic significance [for cancer patients]," Huebner says. "We hope that, in the not-too-distant future, we will be able to compensate for the absence of FHIT [protein]," perhaps with a synthetic version of it, she says.

Seeking the mechanism by which FRA3B is disrupted, LeBeau is studying replication of DNA at the FRA3B site. In cell division, the two intertwined strands of DNA in every chromosome slide apart, and each synthesizes a new strand. However, the DNA at FRA3B is a notoriously late starter. When LeBeau exposes a cell to a chemical that slows DNA replication—as a carcinogen might—she finds that the DNA at FRA3B falls far behind the replication schedule and the cell often divides before FRA3B is ready. As a result, the DNA strands in the new cell may have gaps at FRA3B.

Furthermore, broken DNA strands have ends that are "sticky," Glover says, so they can combine with strand ends of other chromosomes, a process known as recombination. This results in movement of FRA3B DNA, which could disrupt the gene *FHIT* and "could lead to the loss of an important gene" farther out on the chromosome, he says.

A third group of researchers at the Denver conference reported a potential three-way link between the vitamin folate, childhood cancers, and various common fragile sites. A lack of folate, or folic acid, appears to make many fragile DNA sites, including fragile X, more likely to break, but no one yet knows why. Scientists have observed that a mother's low intake of folate during pregnancy increases her baby's risk of brain or spinal cord damage. Folate supplements during pregnancy protect against this defect, and a recent study indicates they may reduce the risk of medulloblastoma, a childhood brain cancer.

Seeking to link these factors, researchers at Genzyme Genetics in Santa Fe, N.M., are investigating whether folate protects against other cancers. In children with leukemia they find that chromosomal breakpoints in cancer cells tend to occur in the vicinity of fragile sites.

Also, the youngest patients are the most likely to have damage to folate-sensitive fragile sites in their cancerous cells, "which is what you might expect if [the cancer] were related to folate levels in pregnancy," says Kathleen E. Richkind, a cytogeneticist at Genzyme. The older a child gets, the more likely it is that carcinogens in the environment play a major role in any cancer that develops, she says. Previous research has shown that leukemia can arise in utero.

These various findings leave an open question: What makes the fragile regions break?

"They could be completely stable until replication is perturbed by an environmental factor," such as tobacco smoke, Glover says. Glover has unpublished data that suggests that smoking boosts the chances that chromosomes will suffer damage at certain fragile sites. □