Bad brakes in cell cycle linked to cancers

Five months ago, molecular biologists tied the tumor suppressor gene p53 to proteins that control the cell cycle – the progression of cells through growth and division (SN: 11/27/93, p.356). Now, two research teams have confirmed an even more insidious relationship between cancer and aberrations in this cycle.

In many tumor types, cells lack functional copies of p16, a protein that puts the brakes on cell division, says Tsutomu Nobori, a molecular biologist at the University of California, San Diego. In these cells, the two copies of the gene that directs production of p16 have either mutated or disappeared, he and his colleagues report in the April 21 NATURE.

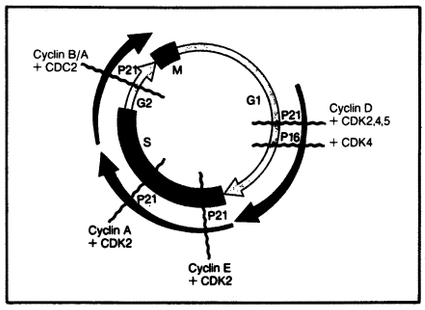
They examined 46 cell lines, or groups of tumor cells, for abnormalities in the region of chromosome 9 where the p16 gene lies. About 61 percent of melanoma cell lines, 87 percent of glioma cell lines, 64 percent of leukemia cell lines, and 36 percent of non-small-cell lung cancer cell lines lacked p16 genes, Nobori reports.

The p16 gene contains three regions that direct p16 production, adds Alexander Kamb, a molecular biologist at Myriad Genetics in Salt Lake City. Independently, Kamb's group studied 12 types of cancers and detected no copies of the p16 gene in 133 of the 290 cell lines tested – a frequency of missing genes similar to that of Nobori's group. In Kamb's report in the April 15 SCIENCE, he has named this gene Multiple Tumor Suppressor 1.

The Utah researchers then analyzed melanoma cell lines for alterations as well as deletions in the p16 gene. With both included, the gene's involvement in cancer increased to 75 percent from 58 percent. They expect this trend to hold for other types of cancers, Kamb says.

"The depth of involvement of this gene [in many cancers] and the frequency with which it pops up tells us that we're really getting at the heart of the [cancer] beast," comments David Beach of the Howard Hughes Medical Institute at Cold Spring Harbor (N.Y.) Laboratory. "[These results] demonstrate clearly that there is a basic defect right at the heart of the cell cycle machinery."

The cell cycle consists of four stages: In the G_1 phase, the cell grows; in S, it makes copies of its chromosomes; in G_2, it prepares to divide; and in M, the nucleus and then the cell divides (see diagram). For a cell to move from one stage to the next, different cyclin proteins must link and activate enzymes called cyclin-dependent kinases (CDK). However, proteins such as p16 and p21 can stop this progression.



C.J. Sherr/adapted from CELL, vol. 73, p.1060

Beach and his colleagues discovered the genes for p16 and p21 last December. It seems that normally, p53 activates the p21 gene whenever a cell's DNA is damaged. The resulting p21 protein freezes the cell cycle until the damage is repaired. It can stop the cell at any point because it inhibits all of the cyclin-CDK complexes that nudge the cell through these various stages of division.

But p16 targets a particular cyclin, one that works at a critical decision-making point in the cycle. At this point, a cell "decides" whether to proliferate, sit tight, or continue to grow but not divide. The researchers hope eventually to be able to influence this decision in tumor cells by adding back the MTS1 gene or administering a drug that mimics p16's braking activity. "It shows finally that all the work we've done for the last 15 years has some clinical relevance," Beach says.

– E. Pennisi

Seizures strike some video gamesters

Now that video games have moved into most U.S. homes and become a daily pastime of many kids, parents have a new disorder to fret over, a recent study suggests.

Among the vast number of video game enthusiasts exists a small group – mostly children – whose brains become overcharged by the experience, causing them to suffer epileptic seizures. A study in the April PEDIATRICS indicates that such reactions occur more frequently than previously thought, though exactly how often remains unknown.

"It seems likely that playing or watching [video games] does not cause normal persons to develop a seizure disorder but only unmasks a peculiar proclivity of the brains of certain individuals," write William D. Graf and his colleagues at the University of Washington School of Medicine in Seattle. They report on 35 video game-related seizure (VGRS) patients, age 1 to 36. Teenage boys make up most of the group. Ten are the authors' patients; the others were described in medical reports dating back to 1981.

Many VGRS patients don't require medication and should simply stay away from video parlors, the authors conclude. "We wanted to tell physicians not to overreact" in treating these kids, Graf says. Such episodes don't usually damage the brain.

Physicians had assumed that only people with unusual electroencephalograms (EEGs) in response to flashing lights are candidates for VGRS, notes Edward J. Hart of North Shore Children's Hospital in Salem, Mass. "That is what I had been telling my patients," he says.

But the new report shows that some of the 35 patients only suffer seizures in response to the games and are not overly sensitive to light. "What we thought was a test [for VGRS] did not seem to hold," Hart says. "That to me is a pretty interesting finding."

Some of the patients may have a rare disorder called reflex epilepsy, in which an unusual stimulus such as a video game or a voice (SN: 7/20/91, p.45) may set off a seizure, agrees Marc R. Nuwer of the University of California, Los Angeles, School of Medicine. Or it could be just coincidence that someone has an episode while playing on such a machine, he argues. But he adds that VGRS usually results from a sensitivity to light.

The Seattle scientists disagree with the coincidence theory. They point out that prior to having a VGRS, most of the patients – 27 – had never suffered a seizure.

All the patients appeared normal on neurological examinations and computed tomographic and magnetic resonance imaging scans. However, some had abnormal EEG readings, suggesting that their brains produce excessive electrical activity in areas that help process light, the researchers say. Also, 17 of 32 people tested had abnormal EEG readings when the researchers flashed a light in their eyes, which indicates light sensitivity.

The most common type of seizure striking video game lovers is a tonic-clonic seizure, once known as a grand mal, which causes people to become stiff and then shake, says Graf. VGRS patients also have simple partial seizures and absences, formerly called petit mals and characterized by seconds-long lapses in consciousness (SN: 7/25/92, p.54).

Patients who remained free of seizures during a 3-year follow-up included 11 of the 15 patients abstaining from video games, 3 of the 6 receiving anticonvulsants but continuing to play, and 7 of the 12 abstaining from the game and taking medication.

Not all the patients took part in the games themselves – three suffered an attack while someone else was playing. The youngest patient in the study, a 1-year-old, had a VGRS while sitting next to her big brother.

– T. Adler