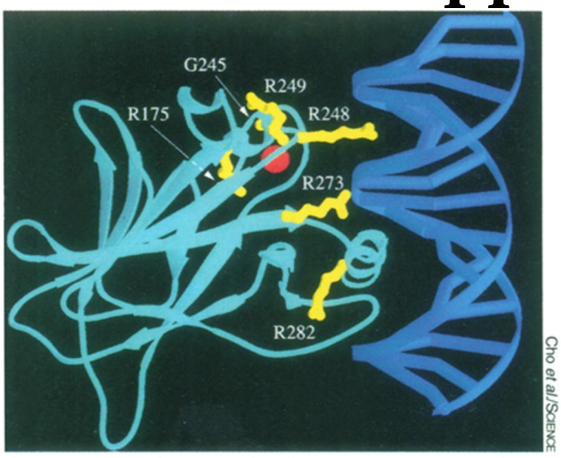
Tumor Suppressor's Structure Revealed



Cho et al/Science

A zinc atom (red) helps shape the section of p53 protein (light blue) that binds to DNA (dark blue), a connection ruined by amino acid changes (yellow).

In cells, a protein called p53 can keep growth in check by binding and activating genes that put the brakes on cell division. Defects in the gene for p53 cause about half of all cancers.

Using two techniques, two groups have now imaged two key sections of the p53 protein, enabling researchers for the first time to see how those genetic defects alter p53's structure. One group, in uncovering how p53 sticks to DNA, discovered that many of the alterations to p53 occur where it attaches to DNA. The other team has shown that p53 acts not alone, but as a foursome.

"With both [studies] together, you actually get a reasonable snapshot of the [p53] molecule," comments Stephen Friend of Massachusetts General Hospital Cancer Center in Charlestown, Mass.

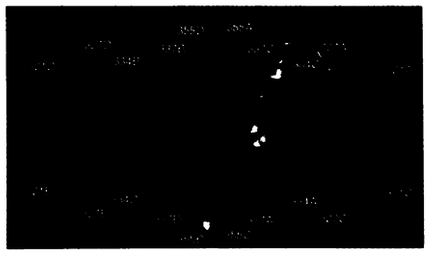
Until now, crystallographers had failed to image p53, in part because the protein contains flexible sections that would not pack closely enough to allow crystals to form. Nikola P. Pavletich and his colleagues at the Memorial Sloan-Kettering Cancer Center in New York City got around this problem by inducing bacteria to make just the section of p53 that binds DNA. Researchers dissolved copies of this section with DNA strands and used X-ray crystallography to study the atoms where the two meet.

Proteins usually bind to DNA in one of three ways. Sometimes, the amino acid arginine will slide into what is called the minor groove in the DNA's helical structure. Other times, the side chains of a few amino acids will reach out and link with phosphates that hang off the DNA. Or, some of the protein's amino acids will twist to form a special helix that interacts with the DNA's helix. "What [p53] has is all these three [mechanisms] combined," says Yunje Cho, also at Sloan-Kettering. "That's never been seen before."

A zinc atom that sits between two amino acid loops stabilizes p53's binding to DNA, Cho and his colleagues report in the July 15 SCIENCE. Most of the other amino acids arrange themselves as strands, four along the upper edge of the section and five along the bottom edge. These act as scaffolding for the few amino acids that actually bind to DNA, Cho notes.

In cells, p53 suppresses the development of tumors only when two p53 molecules pair off and quickly join with another pair, says G. Marius Clore, a biochemist at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md.

Clore and his colleagues used nuclear magnetic resonance spectroscopy to study the atoms where these two pairs joined. Near one end, each copy of p53 has a section of about 40 amino acids that forms these connections. As these sections pair off, a part of each twists into a helix, while another part zigzags to form a sheet. The helices line up, facing opposite ways, then make contact with the two helices from another pair. The resulting foursome consists of a bundle of molecular spirals surrounded by four sheets. The sheets crisscross; altering their angle of overlap changes the spacing between the sections that bind DNA, Clore's group reports in the July 15 SCIENCE.



Clore et al/Science

It takes four p53 proteins to form a functional molecule.

"This sort of structural motif has never been seen before," Clore adds. He suspects that the flexible end of the p53 protein may bend back over the molecule, preventing it from attaching to DNA.

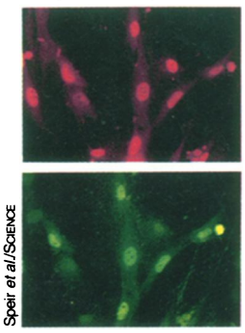
—E. Pennisi

Heart vessel clogs linked to disabled p53

For years, researchers have gathered evidence implicating herpesviruses not only in fever blisters, flu symptoms, and genital sores, but also in coronary artery disease (SN: 4/3/93, p.216). In addition, scientists searching for causes of cancer have tied defects in the tumor suppressor gene p53 to the uncontrolled cell growth that leads to tumors (SN: 11/27/93, p.356).

Now, the paths of those seemingly unrelated investigations have crossed.

Cytomegalovirus, a member of the herpes family, makes a protein that appears to disable the p53 protein. As a result, smooth muscle cells in blood vessels can proliferate until they impede blood flow, explains Edith H. Speir, a cell biologist at the National Heart, Lung, and Blood Institute in Bethesda, Md.



Speir et al/Science

Smooth muscle cells accumulate both p53 (red) and viral protein (green).

She and her colleagues studied why 25 to 50 percent of people who undergo angioplasty—a procedure in which cardiologists insert and inflate a small balloon to unclog heart vessels—return within 6 months, their vessels clogged again. Unlike the initial blockages, which consist of a complex mixture of fatlike substances, debris from blood, and few intact cells, the new ones consist primarily of smooth muscle cells, which may overreact as they repair damage from the angioplasty, Speir explains.

Cardiologists often treat secondary blockages, called coronary restenosis, by removing the clogging clump of cells. Speir's team examined 60 such clumps; they detected p53 in 23 of them. In contrast, they did not find p53 in 20 samples taken from people treated for the first time.

Contrary to what the researchers expected, the p53 genes were perfectly normal, she adds. But almost 80 percent of the clumps with p53 also contained cytomegalovirus. When the researchers later infected smooth muscle cells with this virus, p53 increased in parallel with a viral protein known to stimulate DNA replication, they report in the July 15 SCIENCE. That viral protein may block p53 activity.

Such a link could be expected, says collaborator Eng-Shang Huang of the University of North Carolina at Chapel Hill. "But it will be a surprise to a whole bunch of clinicians," he predicts, adding that this virus may be key in many diseases, including cancer. *—E. Pennisi*