CANCER GENETICS

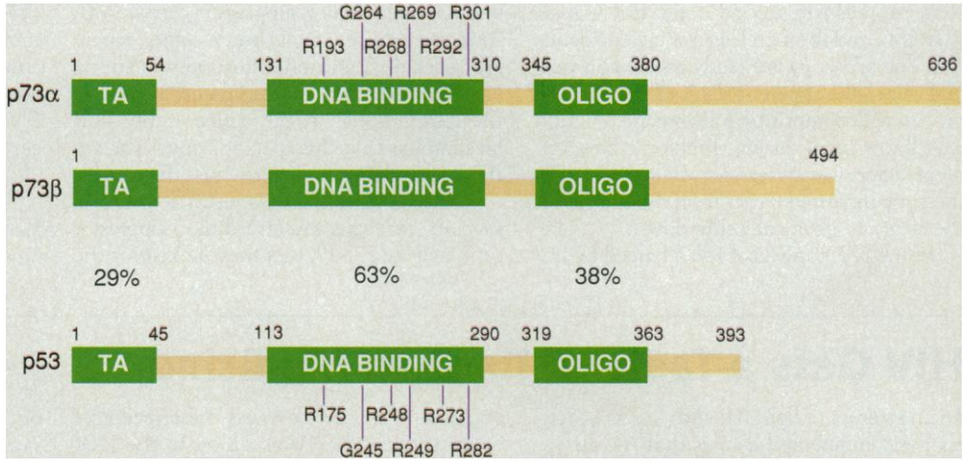
First *p53* Relative May Be a New Tumor Suppressor

In the 20 years since its discovery, the *p53* gene has become one of the most heavily scrutinized genes in history. Indeed, it's referenced in over 8000 papers in Medline, the online biomedical abstract service. The fascination is easy to understand: Loss or inactivation of *p53*, which is a so-called tumor-suppressor gene, is thought to contribute to the development of 50% of all human cancers. All that time, *p53* was thought to be an only child, with no close relatives. Now, researchers have discovered a new gene, a long-lost cousin called *p73*, that bears a strong resemblance to *p53*.

It is being greeted with the same surprise as any newfound relative. "Given the intense interest in this area, the fact that [*p73*] slipped through the cracks is surprising," says cancer biologist Tyler Jacks of the Massachusetts Institute of Technology (MIT). But the new gene should generate some intense interest of its own, because its protein not only resembles the p53 protein, but also seems to have similar activities. The p53 protein acts as a "security guard," deployed when a cell's DNA is damaged to prevent the cell from becoming cancerous. It does this by either inhibiting cell growth until the damage is repaired or causing the cell to commit suicide through a process called programmed cell death or apoptosis. The p73 protein appears to share these growth-inhibiting and apoptosis-promoting effects, although what triggers them and exactly what its cellular role is are both unknown.

Those findings, together with *p73*'s location in a region of chromosome 1 that is often deleted in cancers including neuroblastoma, a malignant tumor of nervous tissue, suggest that it, too, may be a tumor suppressor. "This [discovery] will titillate a whole lot of people," predicts cancer geneticist Bert Vogelstein of Johns Hopkins University School of Medicine, a pioneer of *p53* research. Indeed, if *p73* can stand in for *p53* when that gene is lost, it might be possible to design new cancer drugs that work by turning on *p73* in tumors lacking *p53*.

Molecular biologist Daniel Caput and his colleagues at the pharmaceutical company Sanofi Recherche in Labege, France, identified the *p73* gene while looking for something completely different, namely genes that respond to certain immune system regulators. When the French team sequenced the many potential targets their screen had turned up, they were shocked to find that one false positive had remarkable similarities to *p53*.



F. MCKEON AND ANNIE YANG

No longer alone. The p73 proteins, although longer, resemble p53 in three regions: the transcription activation (TA, 29% identical) and DNA binding domains (63% identical) and also the domain where p53 binds itself (OLIGO, 38% identical). The labeled amino acids indicate residues that are frequently mutated in *p53* and are conserved in *p73*.

As the researchers report in the 22 August issue of *Cell*, the proteins made by *p73* are somewhat larger than p53. But they found that one section of p73 closely resembles the so-called "core binding region" of p53. Many of p53's activities depend on its ability to regulate other genes, and the core binding region is where the protein attaches itself to the DNA when exerting its effects. Of 177 amino acids in that region, 112 are identical. Additional similarities turned up in two other sections thought to be involved in p53 activity—one needed for its gene regulatory effects and another where it apparently binds to itself. These resemblances are enough to suggest that the two genes are the progeny of a gene that was duplicated in some ancient cellular event. Indeed, *p73* may be the ancestral gene, because a gene found in squid that was supposed to be that species's version of *p53* is actually more similar to *p73*.

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>
> **—Bert Vogelstein**

The structural similarities between p53 and p73 also suggested that the proteins might have similar roles in the cell. So Caput and his colleagues joined forces with their longtime collaborator, cell biologist Frank McKeon, who studies gene expression and cell division at Harvard Medical School in Boston, to look for parallels. One way p53 restrains cells that have damaged DNA is by triggering the production of a protein called p21, which blocks cell division. The Caput-McKeon team found that adding *p73* to a line of neuroblastoma that lacks the gene also triggers p21 production, an indication that p73 inhibits cell growth through the same pathway used by p53.

In a paper that appears in this week's issue of *Nature*, molecular biologist William Kaelin at the Dana-Farber Cancer Institute in Boston and his colleagues report similar findings with another tumor cell line. Kaelin's team also found evidence that p73 can mimic p53's ability to cause cell suicide. When overexpressed in these cells, p73 latched onto stretches of DNA to which p53 normally attaches itself when instructing a cell to self-destruct.

Together, the findings suggest that *p73*, too, may be a tumor suppressor, an idea that is buttressed by its provocative chromosomal location. The Caput-McKeon team found *p73* in a region near the tip of chromosome 1 that was already suspected of harboring one or more tumor suppressor genes, because the region is often missing in tumor cells.

The teams did find one major point of difference between the two genes, however. Unlike p53 protein, p73 does not seem to be produced in response to DNA damage. That implies that the protein is not a cell "security guard" the way p53 is. Early results of experi-

ments in which McKeon and Caput deleted the *p73* gene in mice suggest another possibility: It may be "developmentally important," he says, especially in the brain and immune system, although how remains to be clarified.

If *p73* is a tumor suppressor, it may behave somewhat differently than *p53* and other previously discovered tumor suppressors. Classic tumor-suppressor genes require two "hits" to be inactivated—a partial or complete deletion of one of the two gene copies, for example, and another, lesser change that cripples the second copy. But Caput, McKeon, and their colleagues have evidence that one *p73* copy is already inactive in normal cells—the apparent result of a mysterious process called imprinting. Its precise function isn't known, but during embryonic development, imprinting alters certain genes so that the copy inherited either from the mother or the father is specifically shut down.

If one *p73* copy has been silenced by imprinting, then only one hit—loss of the active copy—might be all that it takes to tip a cell into the uncontrolled growth of cancer. Says Kaelin, "*p73* may be the first example of a new paradigm for how tumor-suppressor genes are involved in cancer."

Indeed, molecular biologist Rogier Versteeg of the Academic Medical Center in Amsterdam, the Netherlands, has evidence that an imprinted gene may be involved in neuroblastoma development. He has identified two sites of chromosome damage that contribute to neuroblastoma by knocking out as-yet-undiscovered tumor-suppressor genes. Both lie in the same region of chromosome 1 where *p73* is located, and one illustrates "a strong bias" toward loss from the maternal copy of the chromosome in the cancer cells. This bias implies that this specific copy is the active one and must be lost to cause the cancer.

Other work from the Caput-McKeon team suggests that this mystery tumor-suppressor gene may be *p73*. When they looked for the gene in neuroblastoma cell lines, they found that one *p73* copy had been lost. And while they couldn't uncover any mutations in the remaining copy, most of the cell lines made no detectable p73 protein, implying that the second copy had been silenced by imprinting.

In spite of the differences in the roles of *p53* and its new cousin, both in normal cells and in cancer, the family resemblances may be strong enough for them to substitute for each other. If so, says MIT's Jacks, cancer might be treated by finding a way to switch on *p73* in tumor cells that have lost *p53*. "Even if *p73* is not normally involved in tumor suppression, maybe it could be recruited," says Jacks. Now McKeon and Caput are searching for further family members. But the discovery of *p73* is already certain to captivate their peers.

–Steven Dickman

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AIDS RESEARCH

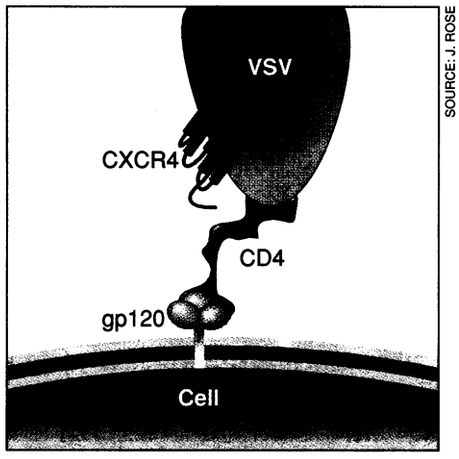
HIV Gets a Taste of Its Own Medicine

In an attempt to fight fire with fire, researchers have engineered a virus that usually infects cattle to attack the AIDS virus in humans. The innovative approach has so far shown promise only in test-tube experiments, but it is attracting widespread attention among AIDS researchers. "It's really on the verge of a breakthrough," says Nava Sarver, who oversees development of novel AIDS treatments at the National Institute of Allergy and Infectious Diseases (NIAID).

Yale University virologist John Rose and co-workers describe in the 5 September issue of *Cell* how they have constructed a potential HIV treatment by modifying vesicular stomatitis virus (VSV), which farmers detest because it causes a mouth infection in cattle that prevents them from eating. As the Yale researchers' experiments show, their newfangled VSV selectively targets and destroys HIV-infected human cells. "It's a pretty interesting way of harnessing a virus for peaceful purposes," says the University of Pennsylvania's Robert Doms. "It's a very clever approach."

The work builds on recent discoveries made by Doms and others about a two-part handshake between HIV and the cells it infects. After HIV binds to the CD4 receptor on a white blood cell, it also must link to another molecule found on the cell's surface, known as a chemokine receptor. Once these handshakes are complete, HIV gains entry, and shortly thereafter, new virus proteins make their way to the cell's outer coating, where they stick out like a flag of victory.

Rose and colleagues reasoned that if VSV could be induced to express these receptors on its surface, they would bind to the HIV proteins displayed on infected cells, turning VSV into a kind of guided missile. To test this idea, the researchers stitched into VSV the genes that code for CD4 and one of HIV's favored chemokine receptors, CXCR4, and added their engineered VSV to a culture containing HIV-infected cells. The virus did, indeed, target just the infected cells, killing them rapidly. "VSV is so fast," says Rose—much faster than HIV, he notes.



SOURCE: J. ROSE

Trojan horse. CD4 and CXCR4 receptors expressed by genetically engineered VSV bind to HIV's gp120 protein on surface of infected cell.

A potential downside to this approach is that the modified VSV might kill cells that aren't infected by HIV. Rose believes that won't happen because he has stripped VSV of its own surface protein, which is what allows it to infect a broad range of cells. "Without its normal coat, it can't infect anything," says Rose. But only animal tests will provide evidence of that, cautions NIAID director Anthony Fauci.

Although Fauci has high praise for the concept's ingenuity, he is concerned that it might take an impracticably high dose of the modified VSV to make a real dent in a person's HIV levels. Another worry, says monkey researcher Ronald Desrosiers of the New England Regional Primate Research Center in Southborough, Massachusetts, is that the body will quickly develop an immune response against VSV, limiting its ability to attack HIV.

Still, Sarver, Fauci, and others are anxious for Rose and colleagues to put their viral guided missile to more stringent test-tube and animal tests. Desrosiers already has begun working with Rose to test the concept in monkeys that have been infected with SIV, HIV's simian cousin. Desrosiers expects to have results in the next few months. Even if they are positive, however, human trials will require the approval of the Food and Drug Administration, which has shown great caution in the past about putting potentially therapeutic viruses into people.

Rose's strategy is not limited to attacking HIV. NIAID's Sarver suggests that if researchers can swap different receptors into this "gutted" VSV, the precisely targeted viruses could be used in everything from vaccines to gene therapies to cancer treatments. "We're not there yet," says Sarver, "but the potential applications are enormous."

–Jon Cohen