New Tumor Suppressor May Rival p53

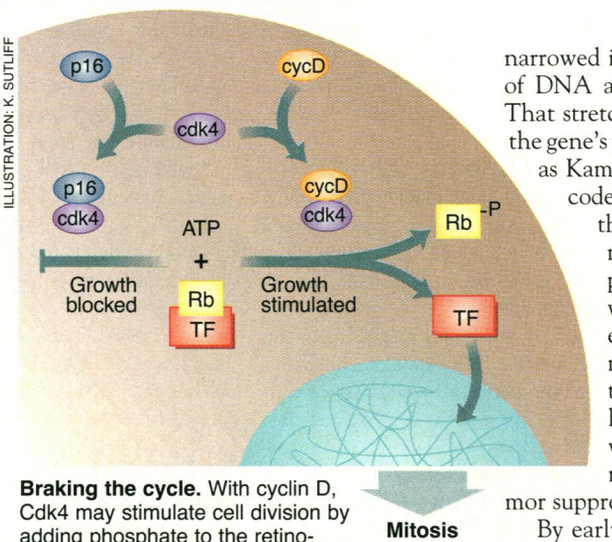
Researchers have the first evidence that an intrinsic component of the cell cycle may be a tumor suppressor—and may perhaps be even more commonly mutated in cancer than p53

If you're tooling along the interstate in your aging Austin-Healy 3000, brake failure can be every bit as catastrophic as a stuck accelerator. And in the last few years, cancer biologists have found that the same principle applies to cell growth: The disastrous accident of cancer can be caused just as readily by the loss of the normal "brakes" on cell growth—the tumor suppressor genes—as by the abnormal activity of the accelerator, the oncogenes. Those findings have made the search for tumor suppressors geneticists' equivalent of the Indy 500, as group after group raced to find and understand new suppressor genes. Now, a team led by molecular geneticists Alexander Kamb of Myriad Genetics, Inc., in Salt Lake City and Mark Skolnick of Myriad and the University of Utah Medical Center has found what appears to be a major new addition to the list of tumor suppressors.

On page 436, Kamb, Skolnick, and their colleagues report that a gene encoding a protein recently identified as an inhibitor of the cell cycle, which drives cells to divide, is deleted or mutated in a wide variety of tumors, including melanomas and bladder, breast, and kidney carcinomas. If the protein, called p16, is a classic tumor suppressor, as these results indicate, it would be of "phenomenal importance," says cancer gene expert Bert Vogelstein of Johns Hopkins University School of Medicine. "It would provide another fundamental link between two one-time disparate areas of research—cell cycle control and cancer genes." (Also see *Science*, 21 January, p. 319.) Indeed, although other tumor suppressors, including the well-known p53, act indirectly through the cell cycle machinery, p16 would be the first intrinsic component of that machinery to be identified as a tumor suppressor.

In addition to forging an even tighter link between two important and extremely active lines of research, the discovery that p16 is a likely tumor suppressor might also have broad practical consequences. Currently, the *p53* gene has the distinction of being the most commonly mutated of all the genes linked to cancer, contributing to the development of as many as 50% of human cancers. But results from the Utah group suggest that *p16* mutations may be even more common contributors to cancer development. "Their claim that it's likely to be more global [than *p53*] is a reasonable one," says tumor suppressor pioneer Eric Stanbridge of the University of California, Irvine, although he cautions that "the jury is still out" on the issue. But if loss of p16 activity does contribute to the development of one or more cancers, it would provide a new target for cancer therapy. It might be possible, for example, to restore normal growth to cancer cells by giving them a good copy of the *p16* gene or by mimicking the effects of the p16 protein with drugs.

ILLUSTRATION: K. SUTLIFF



Braking the cycle. With cyclin D, Cdk4 may stimulate cell division by adding phosphate to the retinoblastoma (Rb) protein, and releasing factors (TF) that turn on genes in the nucleus. But p16 prevents Cdk4 activity.

One indication of the remarkable convergence of cell cycle and cancer gene research is the fact that, when Kamb, Skolnick, and colleagues began their work, they had no inkling they would shortly be delving into the cycle. They did know, however, that they were on the track of a probable tumor suppressor gene. In genetic studies completed in the fall of 1992, the Skolnick group had shown that segment *p21* of chromosome 9 contains a susceptibility gene for the dangerous skin cancer melanoma (*Science*, 13 November 1992, pp. 1080 and 1148). Several researchers had already found abnormalities at *9p21* in melanoma and other cancer cells. And because the abnormalities included deletions—suggesting that loss of a gene from *9p21* might have contributed to the development of the cancers—the group assumed, Kamb says, that the melanoma gene is a suppressor.

That, however, was only a hunch, and the only way to confirm it was to find the gene. By late 1992, the Skolnick team had narrowed its probable location to a stretch of DNA about a million base pairs long. That stretch is still much too long to know the gene's position with any certainty, since, as Kamb notes, a million base pairs can code for as many as 50 genes. To further pinpoint the location, the researchers exploited a detailed physical map of the *9p21* region, which contained some 60 "markers" (essentially sequence landmarks). Kamb and his colleagues then surveyed 100 melanoma cell lines to determine which markers were consistently deleted and might therefore lie within a tumor suppressor gene.

By early this year, they had identified a region that seemed to lie at the center of the deletions, and when they sequenced part of a large cloned DNA corresponding to that region, they immediately hit pay dirt. "We were pleasantly surprised that in one of our first sequencing runs, we picked up an identity to a known sequence," Kamb says. That was none other than the p16 sequence, which had been reported in late 1993 by David Beach's group at Cold Spring Harbor Laboratory on Long Island. "It's quite the great story," says David Morgan, a cell cycle researcher at the University of California, San Francisco. "p16 was poised to have some role [as a tumor suppressor], and along come these guys, and here it is."

The p16 protein was considered a good tumor suppressor candidate because the Beach group had shown that it binds to and inhibits an enzyme called cyclin-dependent kinase 4 (Cdk4), one of several Cdks whose activity propels cells through the cell cycle and into cell division. And by late 1993, there was already a good precedent for Cdk inhibitors as tumor suppressive: Several groups, including those of Vogelstein, Beach, and Morgan, had found that p53 apparently suppresses cell division by stimulating the synthesis of a different Cdk inhibitor, p21.

That wasn't the only clue that p16 might be a tumor suppressor. In addition, it was known that all the Cdks must be activated by proteins called cyclins, and several lines of evidence indicated that one of Cdk4's cyclin partners, cyclin D1, can behave as an oncogene. Taken together, these findings suggest that normal control of cell growth requires a balance between the cyclin acti-

vators of the Cdks and the proteins, such as p16, which inhibit them. As Beach puts it for Cdk4, "The D cyclins are in competition with p16, courting the affection of Cdk4." And anything that leads to overactivity of the Cdks, whether excessive cyclin production or loss of inhibition by proteins such as p16 and p21, can tip cells into the abnormal growth of cancer.

All this evidence led researchers to expect that p16 might be a tumor suppressor. But Kamb says he and his colleagues never expected that it would rival the current champion, p53, as a cancer contributor. The first indications that it might came when the Utah group looked for *p16* deletions in the melanoma cell lines, and later in a wide variety of other kinds of cancer cell lines, a total of 290 in all. Deletions of the gene would indicate that the loss or inactivation of p16 might help cause the cancers.

The results were startling: The researchers found that 50% of the cancer cells displayed deletions in the *p16* gene, as did some primary tumors, an indication that the mutations weren't just lab artifacts. "If you go after a melanoma susceptibility gene, at the end of the day you're surprised if it turns up in 50% of all cancers," Kamb says. In fact, so far, the group has failed to detect *p16* deletions in only two types of cancer: colon cancer and the nerve cell tumor called neuroblastoma. And these findings may well be an underestimate. "The initial screen was very crude," Kamb points out, detecting only large deletions and not subtler changes such as deletions of only a few bases or substitutions of one base for another. When the researchers looked more carefully at their melanoma cell lines, for example, they found that another 25% have such small *p16* mutations—bringing the grand total of mutations in the gene to 75%.

What is more, the Utah group is not alone in seeing *p16* mutations in a wide variety of tumors. Curtis Harris of the National Cancer Institute and Beach confirm that they, too, have similar results, although they are not yet willing to discuss their work in detail because it is still unpublished.

Despite the growing evidence that p16 is a tumor suppressor, the Utah workers do not yet know for sure that they have attained their original goal of identifying the melanoma susceptibility gene. To make sure *p16* is the melanoma gene, they are conducting studies of families in which the skin cancer is hereditary to see whether the members who get the cancer have the expected mutations in *p16*. Also needed is a direct demonstration that introducing a normal *p16* gene into cancer cells in which the gene is mutated can restore normal growth, as would be expected for a tumor suppressor.

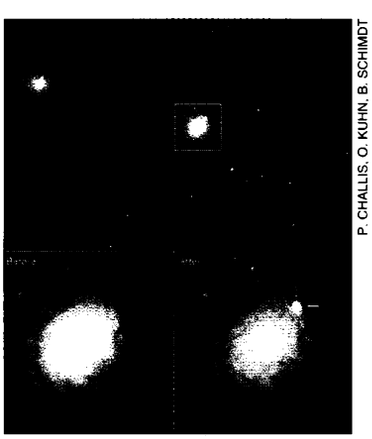
Other researchers won't wait for the results of those studies before extending the Kamb group's work, predicts Stanbridge: "Once this is out, a lot of people will be looking at their favorite tumors to see if [*p16*] is involved." The task will be made only more urgent by the possibility of using the information about *p16* to develop new cancer therapies. "Because the gene is small," says Kamb, "it will be technically easier to work with for gene therapy" than, for example, *p53*, which is four times as large. Also, since p16 currently seems to inhibit only Cdk4, cancer drug developers have a very specific target to shoot at. The prospect of finding such drugs will no doubt help keep attention firmly focused on cellular braking mechanisms as researchers attempt to keep the cell cycle from careering out of control.

–Jean Marx

ASTRONOMY

A Supergiant Dies in the Whirlpool

For supernova researchers, the last few years have brought one treat after another. First, in 1987, the nearest and brightest stellar explosion in more than 300 years flared in the southern sky. Last year came supernova 1993J, which evened the score by giving Northern Hemisphere astronomers their best view of a supernova in decades. And last week, 1994 brought a supernova that, although not quite as bright as last year's, appears to belong to a rare type never before seen in close-up.



P. CHALLIS, O. KUHN, B. SCHMIDT

Out with a bang. Before (7 January) and after (3 April) views of the blast.

The news came, as it did last year, from the amateur supernova hunters who regularly scan the sky for stellar catastrophes. On the night of 1 April, several groups of amateurs in the United States and Japan alerted the rest of the astronomy community to a spot of brightness in the Whirlpool galaxy, M51, an elegant spiral 15 million light-years away. Within days, as the new supernova brightened to its peak and then started to fade, radio and optical telescopes had turned toward the spot and made a preliminary diagnosis.

What the amateurs had spotted was the explosion of a massive star, the same kind of cataclysm responsible for the other bright supernovas. But this year's, designated 1994I, seems to have taken place in a very different kind of star—one so massive and turbulent that it had already blown off its tenuous outer layers and was little more than a naked star core. In coming weeks, astronomers will be watching intently to see how the unusual structure of the progenitor star affects the course of the explosion. "This is the first supernova [of this kind] that is close enough and bright enough...to study in detail," says Kurt Weiler of the Naval Research Laboratory in Washington, D.C.

Initially, some astronomers guessed they were seeing an ordinary type II supernova—the explosion of a massive star within its vast hydrogen envelope, like SN 1987A—or a type Ib, in a massive star that has lost its hydrogen but retains deeper helium layers. But by last Tuesday, Robert Kirshner of Harvard University had taken spectra of the supernova at the Whipple Observatory on Mount Hopkins, Arizona, and found that they showed no sign of hydrogen or helium. "It is pretty clear," says Kirshner, "that it resembles what we call a Type Ic object"—the collapse of a star with perhaps 40 times the mass of the sun. Such supergiant stars are so active, astronomers believe, they can shed their hydrogen and helium in a powerful stellar wind.

The turbulent past of the progenitor star could explain another early observation: the detection of radio signals from the explosion. This finding was made by Weiler and his colleagues, using the Very Large Array in New Mexico, just two days after the discovery—"the earliest anyone has ever detected radio waves from a supernova," says Weiler. He thinks the signals may have been generated as the supernova's fast-moving shock wave slammed into the dense wind expelled from the star just before its explosion.

By Friday, a group led by George Sonneborn of the NASA Goddard Space Flight Center had reported what may be another sign of the progenitor star's history: a burst of ultraviolet emission, detected by the International Ultraviolet Explorer (IUE) satellite. The burst may have been generated, says Kirshner, when energy from the explosion stimulated the surrounding gases. If so, observations he is planning with the Hubble Space Telescope should reveal still more clues to this latest blast's past.

–Ray Jayawardhana

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