Saether of the European Union in Brussels. As a result, Europeans are showing increasing interest in American-style allowance trading. "People come to the United States and want to know how this works and how it is generalizable," says Burtraw.

He notes that the United States succeeded in making the concepts of trading and flexibility hallmarks of the Kyoto agreement to reduce greenhouse gas emissions. And some of the solutions might be similar to those used in the acid rain case: As producers switched to low-sulfur coal, so they might switch to natural gas, which produces less warming per unit of energy produced. Technology and efficiency improvements, particularly in developing nations, might be a relatively cost-effective way to reduce greenhouse gas emissions.

But the parallels are not perfect, Ellerman cautions. For starters, it's not clear that a trading system will work with a half-dozen greenhouse gases, where trades among different industries and across the world would be required. And a key factor in the greenhouse case is the stringency of the emission cap—the final figure of allowable emissions. If it's too low, flexibility is reduced along with the price competition it encourages. As Ellerman and his colleagues have written, emissions trading "is not a panacea that inevitably makes costs of emissions control simply disappear into thin air." But for reining in pollution without choking industry, it looks like a good place to start.

–RICHARD A. KERR

CANCER RESEARCH

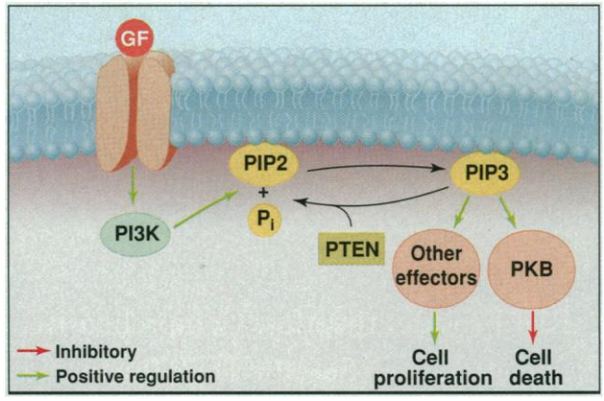
A Surprising Function for the PTEN Tumor Suppressor

The PTEN protein apparently exerts its effects by removing a phosphate from a lipid in one of the cell's key growth control pathways

Last year, cancer researchers welcomed the discovery of the *PTEN* gene with great enthusiasm. Not only was it a new tumor suppressor, one of the growing number of genes whose loss or inactivation contributes to cancer development, but it appeared to be quite an important one: *PTEN* mutations have been linked to a variety of common human cancers, including breast, prostate, and brain cancer (*Science*, 28 March 1997, p. 1876). And unlike some tumor suppressor genes whose functions were complete mysteries when they were first discovered—the two breast cancer genes are examples—*PTEN*'s structure provided an intriguing clue to how the protein might suppress tumor cell growth.

The early reports suggested that PTEN might be a tyrosine phosphatase, an enzyme that strips off phosphate groups attached to tyrosine residues in other proteins. The idea made sense because several oncogenes, which can lead to cancer when inappropriately activated, work by attaching those phosphate groups in the first place, thereby revving up the signaling pathways that tell cells to divide. A protein phosphatase might then be expected to reverse those growth-stimulatory effects. Indeed, cancer researchers had long expected that one or more of the enzymes would prove to be tumor suppressors, but before PTEN's discovery, they had not found any that seemed to fit the bill. Now, a flurry of new papers is showing that they are only half right about how PTEN works.

The enzyme is a phosphatase—but its target is apparently not a protein. Instead, it's a fatty molecule, or lipid, that's tucked into the cell membrane—a completely new kind of target, as far as tumor suppressors are concerned. "It's kind of ironic," notes Ben Neel of Beth Israel Deaconess Medical Center and Harvard Medical School in Boston. "Many of us went into the protein tyrosine phosphatase field looking for tumor suppressors. We finally find a tumor suppressor that looks good—and it turns out to be a lipid phosphatase."



Putting the brakes on. PTEN may inhibit cell growth by removing a phosphate from PIP3, thereby blocking its growth-stimulatory and apoptosis-blocking effects.

The target lipid, called phosphatidylinositol-3,4,5-trisphosphate—PIP3 for short—is a key component of one of the cell's major growth control pathways, acting both to stimulate cell growth and to block apoptosis, a form of cell suicide that can keep damaged cells from proliferating. By stripping away one of PIP3's three phosphates, it appears, PTEN reins in the growth pathways and allows cell suicide to proceed, keeping cell populations in check.

Conversely, loss of *PTEN* during tumorigenesis presumably keeps the PIP3 pathway inappropriately activated, allowing the mutated cells to grow unchecked when they should die. "I think the results are fascinating," says cancer gene expert Bert Vogelstein of Johns Hopkins University School of Medicine in Baltimore. "The new data on lipids dramatically change our perspective and should open up new vistas in the study of oncogenesis."

What's more, knowing that PTEN suppresses proliferation by interfering with the PIP3 pathway may aid the development of treatments for cancers in which *PTEN* is mutated. Such therapies might also control cancers in which the PIP3 pathway is overactive for other reasons. It might be possible, for example, to design drugs that work by blocking critical steps in the pathway.

The first inkling that PTEN might be a lipid phosphatase came in work reported last spring by Jack Dixon, Tomohiko Maehamahis, and their colleagues at the University of Michigan, Ann Arbor. Because the structure of PTEN resembles that of known tyrosine phosphatases, researchers looking for its targets first concentrated on phosphorylated proteins. But Nick Tonks of Cold Spring Harbor Laboratory in New York, a pioneer in the phosphatase field, says that they "had trouble finding any [protein] substrate that made biological sense."

Instead, Tonks and his postdoc Mike Myers found that PTEN preferentially strips phosphate groups from synthetic peptides that carry an unusual number of negatively charged, highly phosphorylated amino acid residues. Such sequences don't occur naturally in any proteins known to be phosphorylated by tyrosine kinases. But the finding prompted both Tonks and Dixon to look at other negatively charged molecules found inside the cell, including phospholipids.

The search paid off: In the 29 May issue of the *Journal of Biological Chemistry*, Dixon's team reported that, in test tube stud-

ILLUSTRATION: K. SUTLIFF

ies, purified PTEN can remove a specific phosphate group from PIP3. Further, when the researchers genetically engineered human cells to produce higher than normal amounts of PTEN, they found that intracellular PIP3 concentrations were lowered. This suggested that the lipid phosphatase activity might play a role in the body.

The discovery immediately pointed to a way in which the enzyme might help control cell growth. PIP3 is well known as an internal messenger for certain cell-growth stimulators, such as insulin and epidermal growth factor. Binding of these molecules to their receptors on the cell membrane activates an enzyme that generates PIP3 by adding a third phosphate to the messenger's predecessor, PIP2. PIP3 in turn activates other kinases in the signaling pathway, including one called Akt, or protein kinase B (PKB). Together, these enzymes encourage cells to enter and progress through the cell division cycle and also keep them from careening into apoptosis. By removing the phosphate from PIP3, PTEN could block this pathway, turning off the growth signal.

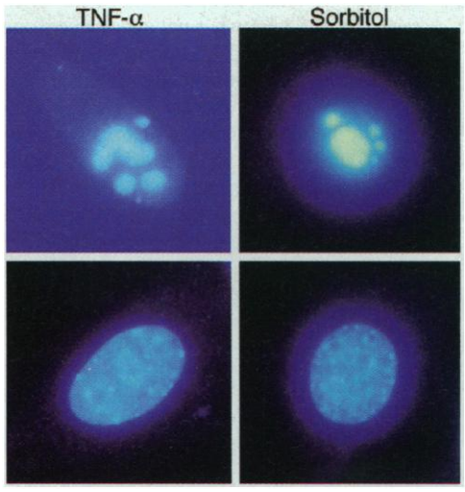
The Dixon team did not show directly that PTEN's lipid phosphatase activity is what makes the enzyme a tumor suppressor, however. More recent work has filled that gap. One clue came from the mutant *PTEN* gene present in a few families with Cowden disease, a rare hereditary disorder whose victims are unusually susceptible to tumors.

Tonks and his colleagues introduced either the normal *PTEN* gene or the Cowden mutant gene into cultured cells derived from a glioma, a type of malignant brain tumor whose uncontrolled growth may be at least partly due to *PTEN* gene inactivation. In a paper in press in the *Proceedings of the National Academy of Sciences*, the researchers report that the normal gene inhibits the growth of the cells. But the gene with the Cowden mutation has lost its ability to prevent the cells from proliferating.

What's special about this mutant PTEN, says Tonks, is that it lacks lipid phosphatase activity, but its protein phosphatase activity remains intact. In a separate paper to appear in the 15 November issue of *Cancer Research*, Webster Cavenee of the Ludwig Institute for Cancer Research at the University of California (UC), San Diego, and his postdoc Frank Furnari present similar results. They, too, have looked at a handful of PTEN mutants, and in a test tube assay have found that every mutation that renders the protein useless as a tumor suppressor eliminates its lipid phosphatase activity. These observations suggest that the lipid phosphatase activity is essential for PTEN's ability to suppress cell growth—a conclusion buttressed by studies of mice in which the *PTEN* gene has been inactivated.

Two groups have produced such knockout mice: One, led by Pier Paolo Pandolfi of Memorial Sloan-Kettering Cancer Center in New York City, published its results in the August issue of *Nature Genetics* and the other, led by Tak Mak of the University of Toronto, describes its mouse in the 22 October issue of *Current Biology*.

Both teams find that mice that can't make any functional PTEN die before birth and that animals that have only one good copy of the gene are more likely than control mice to develop cancers. Mak and his colleagues further report that the tumors, in this case thymic lymphomas, show precisely the abnormalities in the PIP3 signaling pathway that would be expected if PTEN works as postulated. They found, for example, that tumors from these mice show elevated concentrations of phosphorylated, that is, activated, PKB compared to normal thymus tissue. "The difference was night and day," says Mak. "Phosphorylated PKB is just sky high in thymus tumors."



In league with cell death. Cells with one *PTEN* gene *(top)* show typical signs of apoptosis in response to tumor necrosis factor α (TNF-α) and sorbitol, but these agents have no effect on cells lacking a functional *PTEN* gene *(bottom)*.

The same high concentrations of activated PKB—as well as increased amounts of PIP3 itself—show up in embryonic fibroblast cells from the mutant mice, Mak's group reported in the 2 October issue of *Cell*. The researchers also showed that these cells are resistant to cell death induced by such standard apoptosis triggers as ultraviolet radiation, tumor necrosis factor α, or heat shock—a change that might make them more prone to becoming cancerous. Conversely, genetically engineering the mutant fibroblasts with the normal *PTEN* gene restores their sensitivity to the apoptotic signals.

Mak's mouse embryonic fibroblasts provide a "nice, clean system" for studying the function of PTEN, notes David Stokoe of UC San Francisco. But he adds, "at the end of the day, the reason people are studying PTEN is because of its role in cancer," which is why a handful of researchers, including Stokoe, are studying PTEN in human tumor cells. In a report in the 22 October issue of *Current Biology*, Stokoe and his colleagues report that cultured glioma cells have elevated concentrations of PIP3 and activated PKB, just like Mak's fibroblasts. And in September at the CaP CURE conference in Lake Tahoe, Nevada, Charles Sawyers of UC Los Angeles School of Medicine described similar results with prostate cancer cells. "It's a perfect correlation," he says. "In tumor cells that lose PTEN, the PKB pathway is superactive."

Further, researchers have found that adding a normal *PTEN* gene to prostate, glioma, or breast cancer cells reverses these biochemical changes. The teams doing this work include those of Sawyers, Stokoe, and Tonks, as well as those of PTEN's co-discoverers, Peter Steck of the University of Texas M. D. Anderson Cancer Center in Houston and Ramon Parsons of New York City's Columbia University.

It isn't clear, however, whether PTEN normally suppresses tumors by keeping cells responsive to apoptosis signals or by helping to inhibit cell division. Mak's work with fibroblast cells from the *PTEN* knockout mice suggests that the former may be the case, and a group led by Parsons has similar evidence from cancer cells. In an upcoming paper in *Cancer Research*, Parsons and his colleagues show that adding the normal gene for *PTEN* to several breast cancer cell lines causes the cells to undergo apoptosis. Other researchers found that this also happens in prostate cancer cells.

What's more, in a paper scheduled to appear in the 1 December issue of *Cancer Research*, Steck and his colleagues report that glioma cells made to express wild-type *PTEN* are more susceptible to anoikis—a form of apoptosis initiated when an epithelial cell becomes detached from its extracellular matrix. Tumor cells lacking PTEN may thus be better suited to breaking away from the primary cancer and spreading to distant sites in the body.

But in a seemingly contradictory finding, Cavenee and Furnari found that although adding the normal *PTEN* gene to glioma cells suppressed their growth, it did not do so by boosting their rate of death by apoptosis. Instead, the UCSD researchers found that the gene apparently suppresses the growth of glioma cells by inhibiting their progression through the cell cycle, especially when the cells were deprived of serum nutrients. That makes sense, reasons Cavenee, because

SOURCE: STAMBOLIC *ET AL.*, *CELL* 92, 29 (1998)

PTEN mutations often arise in large, late-stage tumors, when cells may be competing to survive in a nutritionally deprived environment. The change would then help them continue to grow anyway.

Although PTEN's link to PKB signaling could explain a lot about its biological behavior, it's obvious that plenty of questions remain. One major issue concerns whether PTEN's effects are entirely due to its lipid phosphatase activity. Researchers so far haven't had much luck in finding protein targets, but they haven't eliminated the possibility that such proteins might be lurking somewhere in the cell.

"We haven't reached the end of the story," predicts Pandolfi, who says he has received dozens of requests for his knockout mice from researchers who want to determine whether their "beloved kinases" are PTEN targets. And that's just fine with Cavenee. "I think we'll see lots of disparate results before we understand what's going on," he says. "To me that makes studying PTEN really interesting." **–KAREN HOPKIN**

Karen Hopkin is a free-lance writer in Bethesda, Maryland.

NEURODEGENERATIVE DISEASES

Alzheimer's Treatments That Work Now

Behavioral interventions developed by social scientists can ease the pain of Alzheimer's disease for both patients and caregivers

Alzheimer's disease is a ruthless decaying of the mind, devastating to those afflicted and to family members who witness their decline. Within the past few years, researchers have made some progress on treatments that might delay the relentless neurodegeneration, but prevention or cure is still out of reach. Millions of people suffer from the disease, and half a million of those in the final stages languish in U.S. nursing homes, incontinent, their bodies frozen by a severe stiffening called contractures, unable to speak or even recognize family members.

While neuroscientists and geneticists search for a way to turn back the clock on the ravages of Alzheimer's, another avenue of research—behavioral research conducted by psychologists, social workers, and nurses—is already providing therapies to relieve some of the suffering of the patients and their caregivers. Such behavioral therapies are far from a cure, and they may not even arrest the underlying disease process. Nevertheless, they represent "an area that cannot be ignored, because we can have such a quick, practical impact on so many people," says Zaven Khachaturian, a former associate director of the Neuroscience and Neuropsychology of Aging Program at the National Institute on Aging who is currently with Khachaturian, Radebaugh, and Associates, an international consulting group on Alzheimer's disease in Potomac, Maryland. Caregivers as well as patients stand to benefit, he notes (see sidebar).

Over the years, Alzheimer's experts have learned that every patient goes through a predictable decline, from forgetfulness at the early stages to an inability to speak and walk as the disease runs its course. Research suggests that patients may lose some abilities faster than necessary because their caregivers underestimate what they can still do for themselves. This is leading to a "use it or lose it" approach to Alzheimer's, in which researchers gauge what patients can still be expected to do and then help them retain those skills. Studies have shown, for example, that behavioral therapy can slow or temporarily halt patients' loss of urinary continence and of their abilities to dress themselves and communicate their needs.

Research done in the past decade also shows that behavioral strategies can reduce many disruptive behaviors common in Alzheimer's patients, such as screaming, wandering, or hitting. In the past, institutions have tried to control such problems by giving the patients antipsychotic drugs or physically restraining them—measures that can cloud the patients' minds even further or increase their agitation. The behavioral approaches instead seek to find the causes of the troubling behaviors and avoid triggering them. "What all this comes to is a new science of Alzheimer's management," says one of the pioneers of the research, New York University (NYU) psychiatrist Barry Reisberg. The next major challenge is to disseminate what researchers are learning to families and community nursing homes outside the orbit of major research centers.

School time. Alzheimer's patients with developmental ages of 2 to 5 learn to brush their teeth at this Madrid day care center.

CREDIT: THE MARIA WOLFF ALZHEIMER CENTER, MADRID

Return to childhood

Many of the recent advances in behavioral therapy arise from viewing Alzheimer's disease as a regression toward infancy. That idea is not new: Aristophanes and Shakespeare both compared old age to a second childhood. But Reisberg and his colleagues recently have established that the stages of Alzheimer's disease accurately mimic such a regression: Patients lose the ability to hold a job, handle finances, pick out clothes, dress and bathe, control their bladder and bowels, and speak, all in faithful reversal of the order those skills were acquired as a child.

As they make this backward march through development, Alzheimer's patients can be assigned "developmental ages." Researchers have found that by providing training appropriate to those ages, they can help the patients retain longer some of the skills they would otherwise lose.

For example, a simple method originally developed to toilet-train retarded children helps Alzheimer's patients maintain continence longer. In the late 1980s, Jack Schnelle of the University of California, Los Angeles, showed that the method called "prompted voiding," in which aides visit patients every 2 to 3 hours to offer to take them to the restroom, helped some incontinent patients retain bladder control. The technique is different from merely taking the patient to the restroom on a schedule, says psychologist Louis Burgio of the University of Alabama, Tuscaloosa, who has studied prompted voiding. By asking whether the patient needs to go, he explains, "it tries to use what is left of the patient's self-knowledge, so you don't make them overly dependent on staff."

Cornelia Beck, a nursing researcher at the University of Arkansas for Medical Sciences in Little Rock, has shown that a similar approach works for another basic activity—dressing. She suspected that patients were losing skills such as dressing and feeding