CANCER BIOLOGY

New Role for Gene Linked to Metastasis Suppression?

Over the past several years researchers have learned a great deal about the many genetic changes that cause cells to slip their normal growth controls and become cancerous. They've identified perhaps 100 oncogenes that can, if they malfunction, produce increased growth. And they've also pinpointed a half-dozen or so genes—the so-called tumor suppressors—that serve to keep potentially cancerous cells in check. By comparison they know relatively little about the genetic changes that give cancer cells their most dangerous characteristic—the ability to metastasize to new sites in the body. And, since researchers are largely in the dark about what causes metastasis, they are hard put to devise new ways to prevent cancers from spreading.

"It's an unusual finding—a protein with an enzyme activity that is also a transcription factor."
—David Levens

That's why the discovery 6 years ago of a gene called *nm23* was greeted with considerable excitement. This gene seems to suppress metastasis in at least some types of cancer, and it might therefore provide a better understanding of what causes cancer cells to spread. Yet *nm23* hasn't been very helpful so far, because its potential metastasis-suppressing mechanism is still poorly understood. Now, a team led by molecular biologist Edith Postel of Princeton University has made a serendipitous discovery that might shed some light on how *nm23* works.

On page 478, Postel and her Princeton colleagues Steve Berberich, Jane Flint, and Cathy Ferrone report evidence suggesting that the protein encoded by one of two closely related human *nm23* genes may be a transcription factor: a protein that turns on gene activity. And in this case the gene that may be turned on is not just any old gene, but the cellular *myc* gene, which is known to have cancer-causing potential.

Both *myc* and *nm23* specialists are intrigued. "I thought the observation was very interesting," says Ken Marcu of the State University of New York at Stony Brook, who has been studying *myc* for several years. "It sets up something totally new." But the Postel team's discovery also creates some paradoxes that researchers can't yet resolve. How, for example, can a gene whose product turns on the *myc* oncogene also be a suppressor of metastasis? That seems backwards.

That puzzle was far from Postel's mind when she happened on *myc*'s possible connection to *nm23*. Her main focus was identifying the proteins that control *myc* activity. During the course of those studies she found a protein that binds to a specific sequence in the gene's regulatory regions and appeared necessary for initiating *myc* gene expression in test-tube assays. Postel called the protein PuF, for purine-binding factor, because the DNA sequence it recognizes has a high content of the purine bases.

To find the gene that encodes PuF, Postel and her colleagues screened a library of human cDNA clones to see if any produce a protein that binds the PuF recognition sequence from *myc*. They found a clone that did and went on to sequence it. When they then searched for a match in the databases, they got an immediate hit: Their PuF gene turned out to be 99% identical to the *nm23-H2* gene, with the few differences located in the noncoding sequences before the start of the gene. Taking her cue from the hockey term for scoring three goals in one game, Postel describes the result as a "hat trick" since it may lead to a better understanding of three outstanding problems: *nm23* gene function, *myc* gene control, and the function of the sequence recognized by PuF/NM23, which occurs in many genes besides *myc*.

The discovery that *nm23* might encode a transcription factor was a surprise because the gene already has a well-established function. Three years ago Marie-Lise Lacombe and Michel Veron of the Pasteur Institute in Paris and their colleagues found that the proteins encoded by these genes function as nucleoside diphosphate (NDP) kinases, enzymes that synthesize GTP and other nucleoside triphosphates by transferring a phosphate from ATP to the corresponding diphosphates (*Science*, 3 August 1990, p. 483). "It's an unusual finding—a protein with an enzyme activity that is also a transcription factor," says another *myc* expert, David Levens of the National Cancer Institute (NCI).

Nevertheless, Levens likes the idea of a protein serving this dual role, since it might explain how changes in gene activity are integrated with corresponding metabolic changes in the cell. For example, the PuF/NM23 protein, acting as a transcription factor, may activate the *myc* gene and, acting as an NDP kinase, may provide the nucleoside triphosphates needed for DNA synthesis before a cell divides. Like many of the other researchers contacted by *Science*, however, Levens stressed the need for more work to confirm the original observation, especially since it was made in a test-tube system, which might not necessarily reflect what happens in living cells.

If it is confirmed, that would still leave the conundrum of how *nm23* could be both a tumor suppressor and an activator of *myc*. *Nm23*'s tumor suppressing properties were first noted by Patricia Steeg and her colleagues at NCI. They found that increased expression of the gene seemed to increase the differentiation of mouse melanoma cells while decreasing their metastatic potential. The NCI workers subsequently observed similar correlations for human breast cancer cells. The mechanism behind this activity is unclear, however. Neither Steeg's group nor Veron's found a correlation between high NDP kinase activity in breast cancer cells and reduced metastatic potential. Indeed, Veron's results led him to conclude that *nm23* might not be a metastasis suppressor after all.

For her part, Steeg cites her own work, plus confirmatory results from several other groups, as supporting the idea that it is. She suggests that the NM23 proteins perform some other function that gives them metastasis-suppressing capabilities. That's why she, too, finds the idea that the PuF/NM23 protein might be a transcription factor "very interesting," although she notes that it's "not immediately obvious" how increasing *myc* transcription fits in with the pattern of *nm23* effects she sees in breast and melanoma cells. One possible explanation for this paradox, Steeg suggests, is that the PuF/NM23 transcription factor might turn on other genes in addition to *myc*. In other types of cancer cells, however, *myc* gene activation by PuF/NM23 would be less surprising. Steeg's group has recently found that in contrast to human breast cancer where high *nm23* expression correlates with reduced aggressiveness and improved survival of the patients, just the opposite occurs in neuroblastomas, a human eye cancer.

If these complications were not enough, there's still another dimension to the *nm23* puzzle: practically all the metastasis work has been done with the *nm23-H1* gene whereas Postel found that PuF is identical to *nm23-H2*. Perhaps only the H1 variant serves as a metastasis suppressor, even though the proteins encoded by the two genes are nearly 90% identical and similar functions would be expected.

For researchers interested in figuring out how *myc* functions, the most pressing need is to confirm that PuF/NM23 is a transcription

factor for *myc* in the cell as well as in the test tube. "What regulates *myc* in vivo is kind of controversial," notes Marcu. That's at least partly due to the fact that the gene is turned on in many different kinds of cells in response to several different growth factors and other stimuli. As a result, Marcu explains, "the gene ends up being somewhat mosaic in the control sequences. This allows it to respond to different players depending on which player is in town." It also makes life difficult for molecular biologists who are studying *myc* gene control, although cloning the PuF gene makes possible a variety of experiments to see if the protein does regulate *myc*.

But even if it doesn't, it might not be the end of the world for PuF/NM23 as a transcription factor. The sequence that binds the protein "is actually pretty common. It occurs in front of a variety of genes," says Levens. "Even if [PuF/NM23] is not used in *myc* control it might still be important" for regulating one or more of the others. While the goal judge hasn't yet signaled a hat trick, Postel's serendipitous finding could at least turn out to be a key assist toward understanding gene regulation.

–Jean Marx

PHYSICS

Coming In Loud and Clear–Via Chaos

When chaos theory was just coming into vogue, in the early 1980s, researchers delighted in its ability to describe with unprecedented mathematical rigor unkempt and seemingly random phenomena such as frost formation and variations in the intervals between heartbeats. But now the field is moving from theory toward application: Physicists and electrical engineers are devising new communication schemes that could harness simple chaotic systems to send private messages or more efficiently transmit information in the clear.

At first blush this may seem surprising, since chaos looks like the antithesis of intelligible communication. But that's precisely the rationale of one scheme, already developed into a working system at the Massachusetts Institute of Technology (MIT), which uses a chaotic signal to mask information in a private transmission. Another group of researchers, though, envisions a way to encode information in the chaotic signal itself by exploiting the hair-trigger sensitivity of chaotic systems to initial conditions. By nudging a chaotic circuit back and forth between two states, such a chaotic transmitter could generate binary code for digital communication.

Even exploiting chaos as a smoke screen isn't straightforward, as electrical engineers Kevin Cuomo and Alan Oppenheim of MIT report in the 5 July *Physical Review Letters*. To turn chaotic circuits into an experimental communication system, they needed a way to faithfully transmit a chaotic signal, which entails synchronizing the complex voltage and current fluctuations of the receiver circuit with those of the transmitter. That's a difficult task: Because of the sensitivity of chaotic systems to small differences in prior conditions, two apparently synchronized systems quickly drift out of step. But in 1989 physicists Louis Pecora and Thomas Carroll of the Naval Research Laboratory showed that certain pairs of distinct chaotic circuits indeed could be synchronized when linked by a common signal.

Simply passing a chaotic signal from one circuit to another, though, is akin to sending and receiving static—not exactly an information-rich exchange, notes Cuomo. To send meaningful messages, the MIT researchers first combine a small information-bearing signal such as a speech waveform with the stronger chaotic signal from the transmitter circuit. Provided the added signal is weak compared to the chaotic signal, the receiver can still regenerate a clean copy of the chaotic portion and subtract it from the raw hybrid signal, unmasking a reasonably faithful copy of the information-bearing component. "The recovered speech is highly intelligible," Cuomo says.

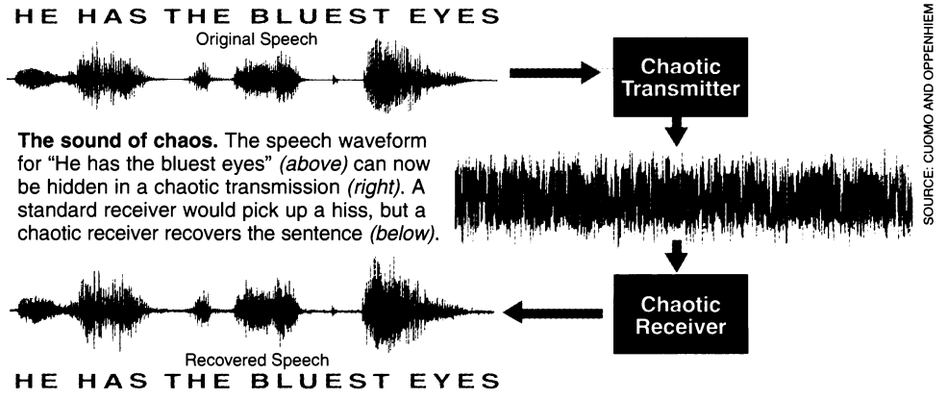
But intelligible only to the receiver, notes physicist Edward Ott of the University of Maryland. Unmasking the information, he says, requires knowing everything about the communications system including details of the circuitry and the specific voltages and currents running through it. "Knowing the system that produces the signal is akin to having the key" to a code, says Ott. A determined eavesdropper equipped with a powerful computer might be able to generate a simulated receiver that could unmask the signal buried in an otherwise chaotic transmission. However, "it probably would take days or weeks or months" to do so, suspects Pecora. "In combat, you may only need a few minutes of privacy or maybe a few days if you're making a business deal over a cellular phone," he says.

If privacy isn't a consideration, a chaotic communicator might turn to the other scheme for harnessing the phenomenon. The high-power oscillators used to generate radio transmissions are prey to instabilities; to keep this chaos at bay, engineers now rely on complex control electronics that limit the power at which the transmitter can be operated. But Ott and his colleagues Celso Grebogi of the University of Maryland and Scott Hayes of the U.S. Army Research Laboratory in Adelphi, Maryland, think there's a way to take advantage of such chaos. In the 17 May *Physical Review Letters*, the researchers suggested that engineers could use microelectronic controls to coax an intelligible message from a chaotic transmitter. Possible payoffs, Ott suggests, would be more efficient transmitters or ones that could broadcast at higher power.

Ott and his colleagues say they are on their way to demonstrating their scheme in a real circuit, but as a proof-of-principle, they tested the effects of very small adjustments to, say, a resistor or amplifier in a so-called double scroll circuit, which they simulated in a computer. Normally, this chaotic circuit fluctuates unpredictably between two states (defined by voltage and current values) that look roughly like a scroll when depicted in a graphical form. But small electrical nudges to the running circuit, the simulations suggested, can steer its output into a pre-chosen pattern of those states, which can correspond to the binary code of a message.

Regardless of the practical payoffs of this early crop of communications schemes, they mark a turning point for the field, Pecora adds. Researchers like Cuomo and Oppenheim "are shifting to synthesizing things," he says. Rather than using chaos theory as a tool for analyzing existing phenomena, they are using it to create new ones.

–Ivan Amato



The sound of chaos. The speech waveform for "He has the bluest eyes" *(above)* can now be hidden in a chaotic transmission *(right)*. A standard receiver would pick up a hiss, but a chaotic receiver recovers the sentence *(below)*.