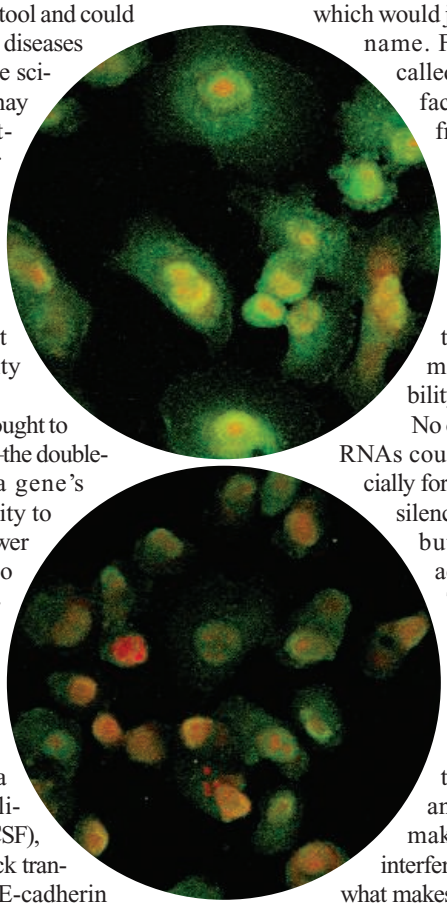
GENETICS

Small RNAs Reveal an Activating Side

The ability of short double strands of RNA to turn off specific genes, a process called RNA interference (RNAi), has enabled new animal models, spawned biotech companies, and a few weeks ago, produced a Nobel prize (*Science*, 6 October 2006, p. 34). Now, a California research team has made the controversial claim that such RNAs can have the opposite effect: They can turn genes on.

This surprising skill—dubbed RNAa, because the RNAs activate genes—is described this week in the online edition of the *Proceedings of the National Academy of Sciences*. If the claim is sustained, RNAa would be a powerful biological tool and could lead to new therapies for diseases such as cancer. But some scientists say the results may reflect an indirect outcome of RNAi, rather than a new way to activate genes. "It's going to be a question of whether this holds up," says Erik Sontheimer, an RNA researcher at Northwestern University in Evanston, Illinois.



New phenomenon? Compared to typical prostate cancer cells (*bottom*), ones administered a short double-stranded RNA (*top*) boost production of a protein (green) encoded by a tumor suppressor gene.

CREDIT: LONG-CHENG LI

RNAi is generally thought to thwart gene translation—the double-strand RNAs cut up a gene's mRNA or block its ability to make protein. But in lower organisms, it can also work at the level of transcription, preventing a gene from even making its mRNA. Long-Cheng Li, a postdoc in the lab of cancer researcher Rajvir Dahiya at the University of California, San Francisco (UCSF), tried to use RNAi to block transcription of the human E-cadherin tumor suppressor gene. When Li added synthetic RNAs that specifically targeted the gene's DNA sequence to human prostate cancer cells, E-cadherin levels unexpectedly went up, not down. "It was immediately quite obvious," Li recalls.

Li then used synthetic RNAs to boost expression of two other genes in cultured cells and now says he can activate numerous tumor suppressor genes with RNAa. If the effect turns out to be predictable, RNAa "could be very powerful, in terms of potential [anticancer] therapeutic application," says John Rossi, an RNA expert at the City of Hope National Medical Center in Duarte, California. Although not every gene is susceptible to RNAa, Li says he's mostly worked out rules for activating those genes that are. He plans to make these rules "readily available to the public" after ironing them out and activating more genes. UCSF has filed for a patent on RNAa.

One key question is whether Li's RNAs are activating genes by silencing others, which would just be RNAi by another name. For example, proteins called negative transcription factors can prevent genes from being transcribed; silencing the genes for these proteins could activate genes they control. Although the UCSF group has not found evidence that this is happening, "formally, that's still a possibility," says Rossi.

No one yet knows how small RNAs could turn genes on, especially for so long. RNAi typically silences genes for 5 to 7 days, but RNAa boosted gene activity for up to 13 days. The molecular machinery underlying RNAi appears to be involved in RNAa, raising the question of how the same enzymes can sometimes turn genes off, and sometimes on. "What makes one siRNA [small interfering RNA] a silencer, and what makes the other one an activator?" asks Sontheimer. "No clue."

Sontheimer also wonders why other groups haven't seen similar gene activation, especially in microarray studies of RNAi that examine thousands of genes. At least four groups have now reported that siRNAs are gene silencers at the level of transcription in mammals, but none have seen gene activation. One of the groups even silenced the gene for E-cadherin, the same one that ▶

Rice Krispies

NEW DELHI—Indian activists have torched the first field trial of a genetically modified food crop. Genetically modified cotton is widely grown in India, but last week, a small field trial of hybrid Bt Rice genetically modified for insect resistance was burnt to ashes at Rampur village in Haryana. It was one of 12 field locations belonging to Maharashtra Hybrid Seeds Company Limited (MAHYCO), Mumbai.

Officials with MAHYCO, owned in part by global seed giant Monsanto, say about 200 activists belonging to the farmers' Bhartiya Kisan Union forced their way into the controlled plot and shouted anti-GM slogans before torching the plot, which was ready to be harvested. Rakesh Tikait, a leader of the group, which is one of several of Indian farmers' groups, told *The Indian Express* that such trials would contaminate the soil and affect yield from existing varieties. "The crop was being grown in isolation as per the [rules], following all safety measures," responds MAHYCO general manager Mahendra Kumar Sharma, who called the attack "deplorable."

Late last month, the nation's Supreme Court put a moratorium on new approvals of genetically modified field releases, and officials must now respond to complaints by activists that permissions had been granted "recklessly." A hearing on the matter is expected next month. **–PALLAVA BAGLA**

Jockeying Planetary Missions

NASA's science budget is tight, but the agency nevertheless approved work on three planetary science proposals—to examine Venus's atmosphere, probe the moon's interior, and return an asteroid sample. Each team gets $1.2 million to provide a more detailed plan for a mission which must cost less than $425 million; the winner will be chosen next year once the studies are complete.

The agency also plans to continue at least one of two missions now in flight. One option would be to redirect the Deep Impact spacecraft that visited Comet Tempel 1 in 2005 to Comet Boethin, to compare the two objects. The other choices would be to focus a camera from the same spacecraft on possible Earth-sized planets around stars, or to send the Stardust spacecraft, to check on changes to Tempel 1 since its encounter with Deep Impact.

"One of the great surprises of comet explorations has been the wide diversity among the different cometary surfaces imaged to date," says Michael A'Hearn, the University of Maryland astronomer who would lead the Boethin mission. **–ANDREW LAWLER**

UCSF turned on. "There's really no indication yet as to why they [at UCSF] see the exact opposite thing," says Sontheimer.

But Rossi—who co-authored one of the silencing papers—says it's possible that he and others missed RNAa because they didn't expect it. "We never did look for upregulation," he admits. And Steve Baylin and Angela Ling, the Johns Hopkins University researchers who silenced the E-cadherin gene with siRNA, find the UCSF report credible. "I'm not sure there's any conflict in the data," says Baylin, who points out that the RNA used by the UCSF group targeted a different part of the gene's sequence from the ones his group employed. "[Gene] region may be the real key."

Fred Gage, a neuroscientist at the Salk Institute for Biological Studies in San Diego, California, calls the UCSF results "intriguing." Two years ago, Gage found a short double-stranded RNA in adult neural stem cells that can activate genes important for neuron function. Gage's activating RNA was naturally made by the cells, while Li used synthetic RNAs. If the UCSF group found similar RNAs in natural systems, that "would take this to another level," Gage said. Li says he now has some evidence for that.

If RNAa is indeed a new phenomenon, researchers trying to exploit RNAi will need to avoid activating other genes beyond the one they're trying to silence, an "off-target" effect that could hamper research applications and new therapies (*Science*, 12 November 2004, p. 1124). But if it does occur naturally, RNAa could provide new insights into gene regulation, adding yet another surprising role to RNA, the molecule of the moment. "If this holds up," says Sontheimer, "it seems there's no end to the number of regulatory mechanisms that small RNAs can access."

–KEN GARBER

Ken Garber is a freelance writer in Ann Arbor, Michigan.

AVIAN INFLUENZA

New H5N1 Strain Emerges in Southern China

A troubling new strain of H5N1 avian influenza has emerged in China over the past year. The group that identified the virus warns that it may be resistant to current poultry vaccines and is possibly now spreading a third wave of bird flu infection across Asia.

International animal health authorities are taking notice but not panicking yet. The emergence of a new, genetically distinct strain "is cause for concern," says Peter Roeder, a virologist with the United Nations' Food and Agriculture Organization (FAO) in Rome. But he adds that claims about its resistance to vaccines "need clarification to justify the conclusions."

Yi Guan, director of the State Key Laboratory of Emerging Infectious Diseases at University of Hong Kong, along with colleagues there and at St. Jude Children's Research Hospital in Memphis, Tennessee, report their findings online this week in the *Proceedings of the National Academy of Sciences*; the paper will appear in the 7 November print edition.

Surveillance. By sampling poultry in markets in southern China, Yi Guan (*center*) and colleagues spotted a new strain of the H5N1 virus.

CREDIT: STATE KEY LABORATORY OF EMERGING INFECTIOUS DISEASES AT UNIVERSITY OF HONG KONG

Guan and his colleagues identified the new strain and a general upswing in overall H5N1 infections through their ongoing surveillance of poultry markets in six provinces of southern China. The team found that from July 2005 through June 2006, the percentage of ducks, geese, and chickens infected with H5N1 climbed to 2.4% of those sampled, up from 0.9% the previous year. The findings suggest the virus remains firmly entrenched in the region, particularly among domestic ducks and geese.

They also found that a new dominant strain had emerged. This H5N1 sublineage, which they call the Fujian strain, was first detected in March 2005 but turned up in only one sample from July to September that year. However, the Fujian strain accounted for 95% of all samples collected from April to June 2006. Several other strains previously circulating in the region dropped off the radar. "It appears that [previous] sublineages have been replaced by this new variant," Guan says.

The researchers found that the hemagglutinin gene from recent human cases reported in China also belonged to the Fujian strain, confirming that it does infect humans. Fujian-like strains were also isolated by other surveillance efforts in Hong Kong, Laos, and Malaysia, indicating it is already spreading beyond southern China.

To check the effectiveness of current vaccines, the group screened blood sera collected from chickens to identify samples from vaccinated animals. They then tested how well 76 of those samples selected at random neutralized three viruses, including the new Fujian strain. Most samples neutralized the older virus strains but had minimal effect on the Fujian strain.

Guan and his colleagues speculate that the new virus may be resistant to current vaccines and that it may have emerged in response to the widespread poultry vaccination in southern China. "Our data show a need to change [currently used] vaccines," Guan says.

Other researchers praise the surveillance effort for spotting the new H5N1 strain. But they are more cautious about the implications for vaccines. Les Sims, a veterinarian based in Manunda, Australia, who advises the FAO on poultry vaccination programs, says, "We recognize that the use of vaccination has the potential for driving antigenic change in these viruses." But he notes that different strains of H5N1 emerged and became dominant even before there was widespread use of vaccines. To demonstrate conclusively that current vaccines aren't working, researchers would need to vaccinate live chickens, infect them with the new strain, and observe the results, Sims adds. Guan agrees and says they are now planning just such an experiment.

Another point on which the two agree is the need to continue postvaccination surveillance efforts—such as Guan's in southern China—to spot and deal with any vaccine-resistant strains that do emerge.

–DENNIS NORMILE

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CORRECTIONS AND CLARIFICATIONS

This Week in *Science*: "Not lost in translation" (1 Dec., p. 1351). The image accompanying this item should have appeared with the preceding item "Turing patterning in the mouse hairs." The image should have been credited to Sick *et al.*

This Week in *Science*: "Making RNA, one molecule at a time" (17 Nov., p. 1045). The second sentence describes RNA polymerase, not RNA, and should begin, "How RNAP translocates relative to DNA in the initial transcribing complex has been controversial…" The next-to-the-last sentence should describe "scrunching" as follows: "RNAP remains fixed on the promoter and pulls downstream DNA into itself."

Reports: "Giant ringlike radio structures around galaxy cluster Abell 3376" by J. Bagchi *et al.* (3 Nov., p. 791). On page 794, column 1, paragraph 2, line 15, the number 50 should be changed to 5, to read "5×10^{19} eV."

Table of Contents: (3 Nov., p. 717). The one-sentence summary for the Report "Protrudin induces neurite formation by directional membrane trafficking" by M. Shirane and K. I. Nakayama was incorrect. It should have read, "Nerve growth factor promotes extension of neurites by local phosphorylation of a newly described protein that then promotes membrane trafficking."

News of the Week: "Small RNAs reveal an activating side" by K. Garber (3 Nov., p. 741). There were two errors in the article. It incorrectly referred to an Angela Ling, when it should have been Angela Ting, and Long-Cheng Li is now an Assistant Researcher at UCSF, not a postdoc.

Policy Forum: "An ambitious, centrist approach to global warming legislation" by D. D. Doniger *et al.* (3 Nov., p. 764). On page 764, the key to the figure misrepresents the options for U.S. CO_2 emission reductions: The red line shows a prompt implementation of emission reductions (450 prompt), and the blue line shows the effects of delayed implementation (-450 delay).

Perspectives: "Cosmic rays track the rotation of the Milky Way" by M. Duldig (20 Oct., p. 429). The first sentence of the first full paragraph on page 430 was incorrect. It should read, "The motion of cosmic rays in a magnetic field is described by a transport equation that takes into account the convection, diffusion, drift, and adiabatic gain (if the field is converging) or loss (if the field diverges)."

News Focus: "AAS High Energy Astrophysics Division: Snapshots from the meeting" by T. Siegfried (20 Oct., p. 411). The item "Galactic jet fuel" describes a finding reported at the meeting by Rita Sambruna of NASA's Goddard Space Flight Center on the composition of jets from active galactic nuclei. Sambruna and collaborators have since discovered a calibration error in their instruments and have retracted their finding.

Table of Contents: (13 Oct., p. 219). The caption for the image that related to the *Science*'s STKE article by S. J. Mulligan and B. A. MacVicar that appeared on the *Science* Online table of contents on page 219 was incorrect. The correct caption is "Communication between astrocytes and neurons."

Reports: "Nonrandom processes maintain diversity in tropical forests" by C. Wills *et al.* (27 Jan., p. 527). The analysis presented in the paper was flawed because of a programming error. The error affects the analysis presented in Table 1 and alters the ordinate of Fig. 4, which was derived from the same analysis. Sentence 2 of paragraph 4 of column 3 of page 529 should read, "Each of these differences consisted of the difference between the observed mortality or recruitment rate of the species in the quadrat and the mortality or recruitment rate of that species in a random sample of the same size taken from that quadrat." Sentences 2 and 3 of the next paragraph should read, "Table 1 lists the average *t* values and degrees of freedom of all these analyses. In most cases, the *t* value was positive and highly significant, but the size of the *t* value diminished as quadrat size increased." Corrected versions of Table 1 and Fig. 4 are shown here with their corrected captions.

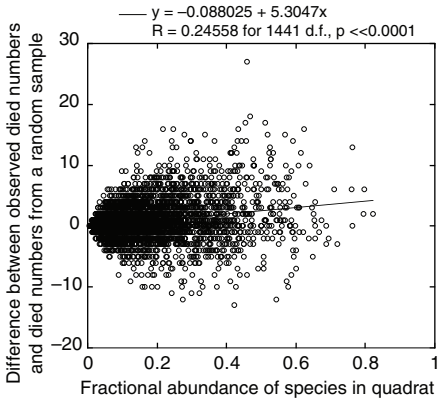

Fig. 4. Plot of Luquillo 10-m quadrat mortality data, in which the frequency of each species in a quadrat (abscissa) is plotted against the difference between the number of trees of the species that died in that quadrat and the number that "died" in a random sample of the same size taken from survivors + died in that quadrat (ordinate). Solid line, linear regression fit to the data.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

	10 m quadrats			20 m quadrats			30 m quadrats			40 m quadrats			50 m quadrats		
	Mean number of trees per species		Paired t-value, *df*	Mean number of trees per species		Paired t-value, *df*	Mean number of trees per species		Paired t-value, *df*	Mean number of trees per species		Paired t-value, *df*	Mean number of trees per species		Paired t-value, *df*
	Real	Random		Real	Random		Real	Random		Real	Random		Real	Random	
Mortality															
Lambir	1.279	1.096	26.0, ***4505***	1.482	1.195	23.9, ***1299***	1.629	1.294	21.7, ***578***	1.747	1.407	19.6, ***325***	1.897	1.539	17.5, ***200***
Pasoh	1.149	1.108	15.3, ***4981***	1.373	1.309	14.1, ***1249***	1.615	1.543	11.7, ***577***	1.917	1.830	10.6, ***324***	2.280	2.188	8.8, ***199***
BCI	1.550	1.435	18.4, ***4971***	2.221	2.082	12.3, ***1249***	2.869	2.740	8.2, ***577***	3.635	3.527	4.8, ***324***	4.544	4.469	2.8, ***199***
Sinharaja	1.490	1.463	2.2, ***2377***	2.101	2.136	–1.3, ***624***	2.792	2.843	–1.2, ***288***	4.072	4.269	–1.5, ***91***	5.522	5.872	–2.1, ***50***
HKK	1.540	1.362	14.0, ***3750***	1.891	1.644	9.4, ***1243***	2.345	2.068	10.0, ***577***	2.880	2.556	11.6, ***324***	3.571	3.209	8.9, ***199***
Luquillo	3.046	2.265	23.0, ***1443***	5.020	3.729	16.0, ***399***	7.091	5.432	12.5, ***186***	9.734	7.598	10.2, ***103***	11.891	9.584	8.1, ***69***
Mudum	2.660	1.908	22.8, ***1696***	3.643	2.076	14.3, ***974***	4.681	2.556	8.1, ***543***	5.532	3.200	9.5, ***318***	6.872	4.142	7.3, ***199***
Recruitment															
Lambir	1.239	1.114	19.6, ***4558***	1.451	1.244	21.0, ***1281***	1.632	1.375	21.7, ***578***	1.849	1.533	19.4, ***325***	2.092	1.719	18.4, ***200***
Pasoh	1.123	1.075	13.3, ***4350***	1.266	1.197	13.9, ***1247***	1.439	1.352	12.6, ***577***	1.635	1.546	10.5, ***324***	1.895	1.789	9.2, ***199***
BCI	1.454	1.353	15.0, ***4816***	2.066	1.903	13.3, ***1249***	2.701	2.490	11.8, ***577***	3.436	3.166	10.5, ***324***	4.299	4.006	8.7, ***199***
Sinharaja	1.440	1.340	5.8, ***1499***	1.811	1.692	4.6, ***559***	2.233	2.089	3.8, ***282***	3.062	2.885	2.4, ***92***	3.970	3.748	2.1, ***51***
HKK	1.975	1.456	19.4, ***2730***	2.442	1.596	14.9, ***1138***	2.947	1.884	14.7, ***567***	3.404	2.268	12.2, ***323***	4.078	2.776	12.8, ***199***
Luquillo	1.771	1.487	11.3, ***1367***	2.530	2.109	8.9, ***397***	3.334	2.874	6.4, ***186***	4.255	3.794	5.0, ***103***	5.162	4.681	4.1, ***69***
Mudum	1.591	1.363	2.7, ***67***	1.694	1.370	3.6, ***84***	1.673	1.370	3.5, ***93***	1.935	1.460	3.3, ***80***	1.815	1.472	2.9, ***79***

Table 1. The mean number of trees per species of trees that died and were recruited in each quadrat was compared with the mean number of trees per species of samples of trees of the same size that were drawn at random from survivors + died or survivors + recruited in the same quadrat. Sampling of all quadrats with two or more trees that died or were recruited was carried out 100 times. The mean *t* values of the paired comparisons between the real and randomized values, along with their degrees of freedom (df), are shown. The expectation was that if trees that died or recruits were a random sample of the trees in the quadrat, there should be no difference in mean numbers of trees per species between the real died or survived categories and the randomized samples from the same quadrats. In almost all cases, the observed mean numbers of trees per species were significantly larger than the mean numbers of trees per species of random samples of the same size. This is the result that would be expected if commoner species were overrepresented and rarer species underrepresented among the trees that died and the trees that were recruited. The significance of the difference between real and random data sets diminished with increasing quadrat size, as expected if the nonrandom effects were strongest in the local regions represented by small quadrat sizes.

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