CANCER GENETICS

A Detailed Genetic Portrait of the Deadliest Human Cancers

Three studies published this week have given researchers their most detailed look so far at the genetic mutations that underlie the deadliest of human cancers: pancreatic cancer and the brain tumor glioblastoma. They have firmed up the role of key genes and also found that scores of aberrant genes are involved in relatively few cell signaling pathways. One study also unearthed a gene never before linked to cancer that is mutated in a substantial fraction of glioblastoma tumors. "It shows we can still be surprised" by the biology of cancer, says Michael Stratton, who oversees a cancer gene sequencing project at the Sanger Institute in Hinxton, U.K.

These studies are all based on the premise that information gleaned from systematically cataloging the main mutations in tumors will be worth the high cost. Three years ago, when genome sequencer Eric Lander of the Broad Institute in Cambridge, Massachusetts, proposed spending $1.5 billion on what is now called The Cancer Genome Atlas (TCGA), skeptics helped persuade the U.S. National Institutes of Health to start with a 3-year, $100 million pilot project. One of the glioblastoma studies is the first fruit of that effort.

Meanwhile, a team led by Bert Vogelstein, Kenneth Kinzler, and Victor Velculescu at Johns Hopkins University in Baltimore, Maryland, had begun a private cancer genome project, starting with breast and colorectal cancer (*Science*, 8 September 2006, p. 1370). Now this team and collaborators have sequenced the coding regions of 20,700 genes—nearly all the known genes in the human genome—in 22 glioblastoma and 24 pancreatic cancer samples. They also looked for abnormalities in gene copy number and gene expression.

In two papers published online by *Science* this week (www.sciencemag.org/cgi/content/abstract/1164382 and -1164368), they report finding hundreds of genes that were mutated in these two cancers. There were an average of 63 altered genes in each pancreatic tumor and 60 per glioblastoma. The mutations varied from tumor to tumor, but the most important tended to fall in the same cell pathways. For example, 12 specific pathways were disrupted in at least 70% of pancreatic tumors. "It points to a new way of looking at cancer," says Vogelstein, who suggests that treatments should target these pathways, not the products of single genes.

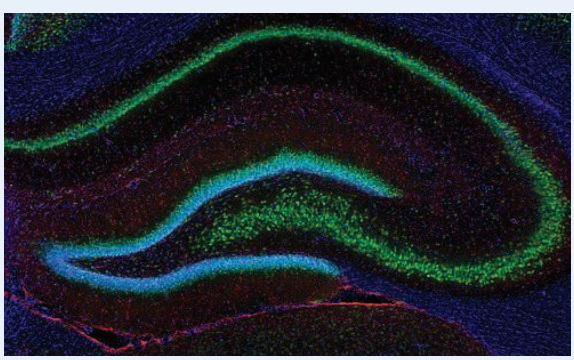
One of the altered genes found in the glioblastoma study, *IDH1*, appeared in 12% of tumors, and more often in younger patients and those with secondary tumors, the Johns Hopkins team reported. A change in an amino acid of the encoded protein seems to help patients with this mutation live longer than others with glioblastoma.

The third study, published online by *Nature*, analyzed more than 200 glioblastoma samples. It surveyed all the samples for genetic alterations such as changes in copy number and probed about half the samples for mutations in 600 genes already implicated in cancer, says co-leader Lynda Chin of the Dana-Farber Cancer Institute in Boston (*Science*, 4 July, p. 26). The study found many of the same aberrant

NEUROSCIENCE

Hippocampal Firing Patterns Linked to Memory Recall

The hippocampus, tucked deep inside the temporal lobes of the brain, has been intensely studied for its role in recording memories. Now two studies—one with rats and one with people undergoing surgery for intractable epilepsy—suggest that patterns of neuron firing in the hippocampus are also involved in recalling past experiences.



Memory aid. A rat's hippocampus (*above*) generates sequences of neural firing that may help it remember what to do next.

CREDIT: NEAL MELVIN/2007 OLYMPUS BIOSCAPES COMPETITION (HONORABLE MENTION)

"The two papers are significant because they point directly to reactivation of neural activity sequences as a mechanism for memory recall," says Edvard Moser, a neuroscientist at the Norwegian University of Science and Technology in Trondheim. Such a mechanism may underlie several functions attributed to the hippocampus, Moser says, including navigation, memory, and planning future actions.

In the rat study, researchers led by Eva Pastalkova and György Buzsáki of Rutgers University in Newark, New Jersey, simultaneously recorded the activity of scores of hippocampal neurons as rodents ran through a maze shaped like a squared-off figure eight. The rats always started the maze by running down the middle of the three arms and then chose to continue down either the left or the right arm. The researchers trained them to alternate between the right and left arms each time they ran the maze. In between runs, the rats spent 10 to 20 seconds on a running wheel.

During this delay period, neurons in the hippocampus fired in sequences that predicted which arm the rat would run next, the researchers report on page 1322. Even in the few cases when a rat goofed and went the wrong way, the preceding firing sequence predicted its mistake. These sequences—which resemble sequences that occur as a rat actually runs through a maze—likely represent the brain's internal mechanism for planning (or reminding itself) what it has to do next, Buzsáki says.

The findings confirm a decade-old prediction that the hippocampus might generate such firing sequences to maintain important information during a delay in a task, says David Redish, a neuroscientist at the University of Minnesota, Minneapolis. Redish notes that consistent patterns of activity emerged only when the rat had something to remember. "When the rat is just running on

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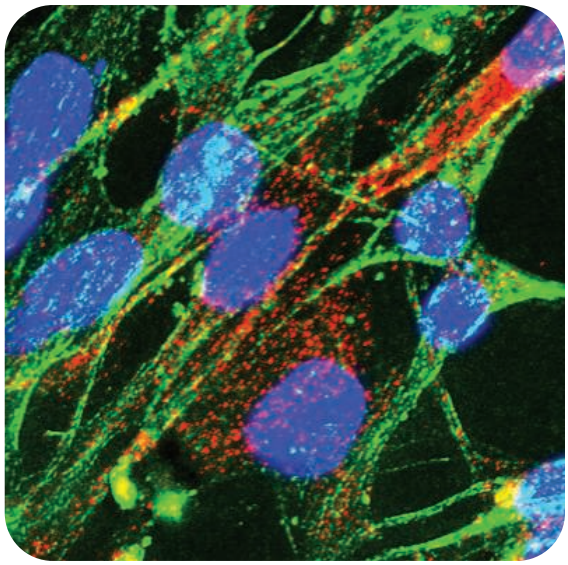

Probing a killer. Two new studies tally genetic glitches that cause the brain tumor known as glioblastoma, orange in this image of brain cells.

genes that the Johns Hopkins team uncovered—but not *IDH1*, which was not among the genes the team sequenced. Their larger sample set will serve as a reliable reference on how frequently mutations occur in glioblastoma, including several genes for which the evidence was limited until now, says Chin. Having methylation data and samples from patients who received treatment also allowed the team to finger mutations in DNA repair genes that may help explain why tumors that initially respond to temozolomide, the main drug for glioblastoma, can become resistant to subsequent therapies.

TCGA is preparing follow-on papers, for example on using the molecular data to classify subsets of tumors, Chin notes. It will also expand the search: The project, which is also studying lung and ovarian cancers, will use new technologies to sequence thousands of genes in each tumor.

"I see them [the public and private glioblastoma studies] as wonderfully complementary," says pathologist Paul Mischel of the University of California, Los Angeles, who studies glioblastoma. Other researchers who hope to use the findings to improve cancer treatment agree. "This is a start and a wonderful start," says Santosh Kesari, a neurooncologist at Dana-Farber.

–JOCELYN KAISER

a wheel for the heck of it in its home cage, they don't see it."

In the human study, published online this week in *Science* (www.sciencemag.org/cgi/content/abstract/1164685), researchers led by Hagar Gelbard-Sagiv of the Weizmann Institute of Science in Rehovot, Israel, and Itzhak Fried of the University of California, Los Angeles, recorded from hundreds of neurons in and around the hippocampus of 13 epilepsy patients undergoing operations in which surgeons introduced electrodes into the brain to locate the source of their seizures. The patients watched several 5- to 10-second video clips that depicted a variety of landmarks, people, and animals. A few minutes later, the researchers asked the patients to freely recall the clips they'd just seen and call them out as they came to mind. (Most subjects easily remembered almost all of the clips.) The first time the patients saw the clips, many neurons in the hippocampus and a nearby region, the entorhinal cortex, responded strongly to certain clips and weakly to others—preferring a clip from *The Simpsons*, say, to ones showing Elvis or Michael Jordan. Later, each neuron began firing strongly a second or two before the subject reported recalling that neuron's preferred clip, but not when the subject recalled another clip.

"Previous work [with animals] has shown that such reactivation occurs during sleep as well as during certain behaviors where memory is needed, but it has remained unclear whether reactivation actually reflects recall of the memory," say Moser. Fried's findings are exciting because they provide the first direct link between reactivation of hippocampal neurons and conscious recall of a past experience, says neuroscientist Matthew Wilson of the Massachusetts Institute of Technology in Cambridge.

Both studies have implications for an ongoing debate about the relationships among various functions attributed to the hippocampus, says Lynn Nadel, a neuroscientist at the University of Arizona in Tucson. Nadel says that the findings fit with his view that the neural mechanisms underlying spatial navigation, episodic memory, and action planning may be one and the same. "One might say at this point that the available data suggest that the hippocampus is critical for 'navigating' through space not only in the present but also in the past, to retrieve memories, and in the future, to predict the results of actions," Nadel says.

–GREG MILLER

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Japanese Budget Rollout

TOKYO—Japan's education ministry last week optimistically called for boosting fiscal 2009 science spending a hefty 13.4% year-on-year to $24.1 billion. The ministry wants to add $20 million, a 12.4% increase, for academic research grants and 11% more—for a total of $1.2 billion—to advance big science projects, including $41 million for Japan's contribution to the international Atacama Large Millimeter Array in Chile. Applied research fared even better. The ministry wants to increase one such grant category, for example, by 42%, to $4.5 million. The proposed budget faces scrutiny from the budget-minded finance ministry. "Negotiations will be tough, but we'll do our best," says Shinichiro Izumi of the education ministry. The budget, which takes effect in April, will be finalized by January.

–DENNIS NORMILE

Taleyarkhan Weighs Suit

Rusi Taleyarkhan, the Purdue University nuclear engineer deemed guilty of research misconduct, isn't going quietly. Last week, Purdue stripped him of his named professorship. Now, Taleyarkhan and his attorney are considering filing a grievance with Purdue, a lawsuit against the school, or both. "The process and the manner in which Purdue has carried itself … is testimony for the need to resort to the court system," Taleyarkhan wrote in an e-mail to *Science*. In 2002, Taleyarkhan and colleagues reported that a tabletop device generated nuclear fusion inside collapsing bubbles. But in July, an investigation organized by Purdue concluded that later reports aimed at replicating the work involved research misconduct. Taleyarkhan's attorney says the scientist will continue to investigate bubble fusion.

–ROBERT SERVICE

Your Local Library

The U.S. National Institutes of Health (NIH) has chosen nine screening centers in the second phase of its Molecular Libraries program (*Science*, 8 August, p. 764). NIH wants to test biological assays submitted by researchers against 300,000 chemicals in hopes of finding research probes and drug leads. Four major centers will receive a total of $208 million over 4 years—the Burnham Institute for Medical Research and The Scripps Research Institute, both in San Diego, California; NIH's intramural center in Rockville, Maryland; and the Broad Institute in Cambridge, Massachusetts. NIH will also support five smaller centers.

–JOCELYN KAISER

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