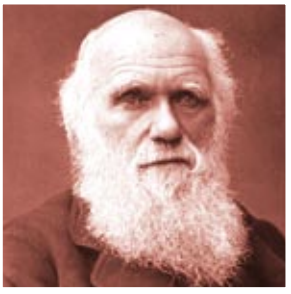
EVOLVED FOR CANCER?

BY CARL ZIMMER

Natural selection lacks the power to erase cancer from our species and, some scientists argue, may even have provided tools that help tumors grow



Charles Darwin, 1881

RICHARD MILNER ARCHIVES

NATURAL SELECTION IS NOT NATURAL PERFECTION. Living creatures have evolved some remarkably complex adaptations, but we are still very vulnerable to disease. Among the most tragic of those ills—and perhaps most enigmatic—is cancer. A cancerous tumor is exquisitely well adapted for survival in its own grotesque way. Its cells continue to divide long after ordinary cells would stop. They destroy surrounding tissues to make room for themselves, and they trick the body into supplying them with energy to grow even larger. But the tumors that afflict us are not foreign parasites that have acquired sophisticated strategies for attacking our bodies. They are made of our own cells, turned against us. Nor is cancer some bizarre rarity: a woman in the U.S. has a 39 percent chance of being diagnosed with some type of cancer in her lifetime. A man has a 45 percent chance.

NATURAL SELECTION HAS FAVORED CERTAIN DEFENSES AGAINST CANCER BUT CANNOT ELIMINATE IT ALTOGETHER.

These facts make cancer a grim yet fascinating puzzle for evolutionary biologists. If natural selection is powerful enough to produce complex adaptations, from the eye to the immune system, why has it been unable to wipe out cancer? The answer, these investigators argue, lies in the evolutionary process itself. Natural selection has favored certain defenses against cancer but cannot eliminate it altogether. Ironically, natural selection may even inadvertently provide some of the tools that cancer cells can use to grow.

The study of cancer evolution is still in its infancy, with much debate about the mechanisms involved and much testing of hypotheses left to carry out. Some medical researchers remain skeptical that the work will affect the way they fight the disease. Evolutionary biologists agree that they are not about to discover a cure for cancer, but they argue that understanding cancer's history could reveal clues that would otherwise remain hidden. "Obviously, we always have that in the back of our minds in everything we do," says Judith Campisi of Lawrence Berkeley National Laboratory.

The Dawn of Cancer

AT ITS ROOT, cancer is a disease of multicellularity. Our single-celled ancestors reproduced by dividing in two. After animals emerged, about 700 million years ago, the cells inside their bodies continued to reproduce by dividing, using the molecular machinery they inherited from their progenitors. The cells also began to specialize as they divided, forming different tissues. The complex, multicellular bodies animals have today were made possible by the emergence of new genes that could control how cells divided—such as by stopping the cells' reproduction once an organ reached its adult size. The millions of animal species are evidence of the great evolutionary success that came with acquiring a body. But bodies also present a profound risk. Whenever a cell inside a body divides, its DNA has a small chance of acquiring a cancer-causing mutation. "Every time a cell divides, it's going to be at risk of developing into cancer," Campisi says.

Rare mutations, for instance, may cause a cell to lose restraint and begin to multiply uncontrollably. Other mutations can add to the problem: They may allow deranged cells to invade surrounding tissues and spread through the body. Or they may allow tumor cells to evade the immune system or attract blood vessels that can supply fresh oxygen.

Cancer, in other words, re-creates within our own bodies the evolutionary process that enables animals to adapt to their environment. At the level of organisms, natural selection operates when genetic mutations cause some organisms to have more reproductive success than others; the mutations get "selected" in the sense that they persist and become more common in future generations. In cancer, cells play the role of organisms. Cancer-causing changes to DNA cause some cells to reproduce more effectively than ordinary ones. And even within a single tumor, more adapted cells may outcompete less successful ones. "It's like Darwinian evolution, except that it happens within one organ," explains Natalia Komarova of the University of California, Irvine.

Limits to Defenses

ALTHOUGH OUR BODIES may be vulnerable to cancer, they also have many ways to halt it. These strategies probably resulted from natural selection, because mutations that made our ancestors less likely to die of cancer in their prime could have raised their reproductive success. But given the many millions of people who get cancer every year, it is obvious that these defenses have not eradicated the disease. By studying the evolution of these defenses, biologists are trying to understand why they fall short.

Tumor suppressor proteins are among the most effective defenses against cancer. Studies suggest that some of these proteins prevent cancer by monitoring how a cell reproduces. If the cell multiplies in an abnormal way, the proteins induce it to die or to slip into senescence, a kind of early retirement. The cell survives, but it can no longer divide. Tumor sup-

Overview/*Cancer Evolution*

- Natural selection has only a limited ability to prevent cancer. It has provided some defenses, but these tend to delay the disease until late in life rather than eliminating it entirely.
- In addition, evolutionary forces have apparently favored some genes that can contribute to cancer's development or aggressiveness.
- An understanding of cancer's evolutionary history—and how individual tumors evolve in the body—could suggest fresh angles of attack on the disorder.

pressor proteins play a vital role in our survival, but scientists have recently discovered something strange about them: in some respects, we would be better off without them.

Norman E. Sharpless of the University of North Carolina at Chapel Hill genetically engineered mice to study the effect of one of these proteins, called p16 (or, more properly, p16-Ink4a). He and his colleagues created a line of mice that lacked a functional gene for p16 and thus could not produce the protein. In September 2006 the group published three studies on the mice. As expected, the animals were more prone to cancer, which could arise when they were only a year old.

But losing the p16 gene had an upside. When the mice got old, their cells still behaved as if they were young. In one experiment, the scientists studied older mice, some of which had working p16 genes and some of which did not. They destroyed insulin-producing cells in the pancreases of the animals. The normal rodents could no longer produce insulin and developed fatal diabetes. But the ones without the p16 protein developed only mild diabetes and survived. The progenitors of their insulin-producing cells could still multiply quickly, and they repopulated the pancreas with new cells. The scientists found similar results when they examined cells in the blood and brains of the mice: p16 protected them against cancer but also made them old.

These results support a hypothesis Campisi has developed over the past few years. Natural selection favors anticancer proteins such as p16, but only in moderation. If these proteins become too aggressive, they can create their own threats to health by making bodies age too quickly. "It's still a working hypothesis," Campisi admits, "but the data are looking stronger and stronger."

Delaying the Inevitable

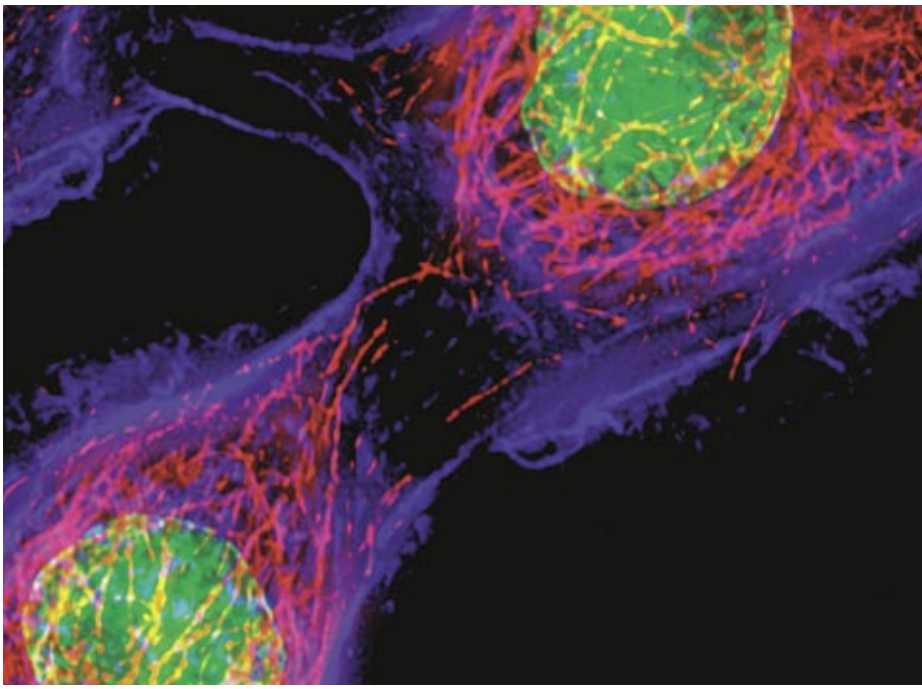
A DEFENSE AGAINST CANCER does not have to eradicate the disease completely to be favored by natural selection. If it can just delay tumors until old age, it may allow people to have more children, on average, than others who lack the defense. It may seem cruel for evolution to stick old people with cancer, but as Jarle Breivik of the University of Oslo points out, "natural selection does not favor genes because they let us live long and happy lives. They are selected for their ability to propagate their information through the generations."

Anticancer proteins such as p16 may favor the young over the old. When p16 pushes a cell into senescence, the cell does not just stop multiplying. It also begins producing an odd balance of proteins. Among the proteins it makes is vascular endothelial growth factor (VEGF), which triggers the growth of more blood vessels. VEGF fosters the growth of tumors by supplying them with extra nutrients. In young people, p16's main effect may be to suppress cancerous cells. But over time, it may create a growing population of senescent cells, which could make people more vulnerable to cancer in old age.

Another way to delay cancer is to set up several lines of defense. Studies on colon cancer, for example, show that cells in the colon must acquire mutations to several genes before they turn cancerous. These defense lines do not prevent people from getting colon cancer—in fact, it is the third most common form of the disease. But the need for multiple mutations to occur in a cell may reduce the chances that colon cancer will arise in young individuals. The average age of people diagnosed with colon cancer is 70.

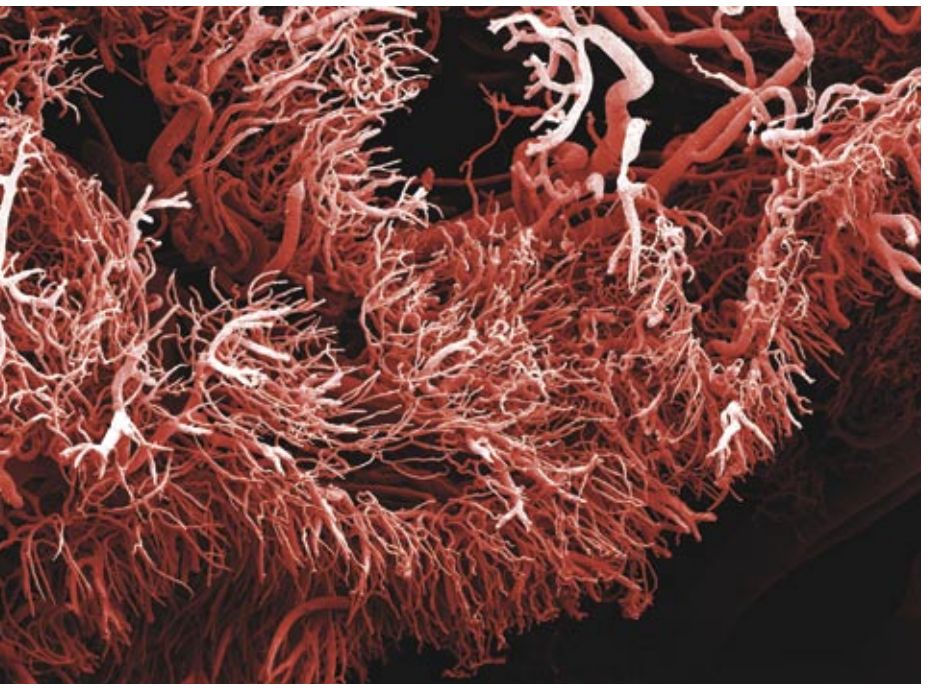
Not all cancers strike the old, of course. Most victims of a cancer of the retina called retinoblastoma, for example, are children. But Leonard Nunney of the University of California, Riverside, argues that evolution is responsible for that difference between the

Cell in the final stage of division



PAUL ANDREWS University of Dundee/Photo Researchers, Inc.

"EVERY TIME A CELL DIVIDES, IT'S GOING TO BE AT RISK OF DEVELOPING INTO CANCER."
—Judith Campisi



Resin cast of blood vessels in a tumor

THE ABILITY TO STIMULATE NEW BLOOD VESSEL FORMATION SERVES A TUMOR JUST AS IT DOES A PLACENTA.

two cancers. Nunney points out that colon cells have many more opportunities for acquiring dangerous mutations than retinal cells do. The colon is a large organ made of many cells, which continue replicating throughout a person's life as old cells slough off and new ones take their place. That risk puts a big evolutionary premium on defenses that can prevent colon cells from turning cancerous.

The retina, on the other hand, is "the smallest bit of tissue you can imagine," as Nunney puts it. That small set of retinal cells also stops multiplying by the time a child turns five. With fewer cell divisions occurring, the retina has far fewer opportunities to turn cancerous. As a result, retinoblastoma is extremely rare, striking only four people in a million. Because the risk is so much lower, Nunney argues, natural selection cannot drive the spread of new defenses against retinoblastoma. A defense against cancer in the retina would make very little difference to the average reproductive success of a population.

THE AUTHOR

CARL ZIMMER writes frequently about evolution for the *New York Times, National Geographic* and other publications. He is the author of five books, including *Parasite Rex* and *Soul Made Flesh*. He is now working on a book about *Escherichia coli* and the meaning of life. His blog, The Loom (www.scienceblogs.com/loom), is a winner of *Scientific American*'s Science and Technology Web Awards. Zimmer wrote about the neurobiology of the self in the November 2005 issue of *Scientific American*.

Making Tools for Tumors

RECENT RESEARCH SUGGESTS that natural selection may have altered genes in ways that make cancer cells more dangerous. Evolutionary biologists discovered this disturbing possibility as they searched for the changes that have made us uniquely human. After our ancestors diverged from other apes about six million years ago, they experienced natural selection as they adapted to a new way of life as a toolmaking, savanna-walking hominid. Scientists can distinguish between genes that have not changed significantly since the origin of hominids and those that have undergone major alteration as a result of selection pressures. It turns out that among the genes that have changed most dramatically are some that play important roles in cancer.

Scientists suspect that the adaptive advantages brought by these genes outweigh the harm they may cause. One of these highly evolved cancer genes makes a protein called fatty acid synthase (FAS). Normal cells use the protein encoded by this gene to make some of their fatty acids, which are used for many functions, such as building membranes and storing energy. In tumors, however, cancer cells produce FAS protein at a much higher rate. The protein is so important to them that blocking the activity of the gene can kill cancer cells. By comparing the sequence of the FAS gene in humans and other mammals, Mary J. O'Connell of Dublin City University and James McInerney of the National University of Ireland found that the gene has undergone strong natural selection in humans. "This gene has really changed in our lineage," McInerney says.

McInerney cannot say what FAS does differently in humans, but he is intrigued by a hypothesis put forward by the late psychiatrist David Horrobin in the 1990s. Horrobin argued that the dramatic increase in the size and power of the human brain was made possible by the advent of new kinds of fatty acids. Neurons need fatty acids to build membranes and make connections. "One of the things that might allow a larger brain size was our ability to synthesize fats," McInerney speculates. But with that new ability may have come a new tool that cancer cells could borrow for their own ends. Cancer cells may, for

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example, use FAS as an extra source of energy.

Many fast-evolving cancer genes normally produce proteins in tissues involved in reproduction—in the placenta, for example. Bernard Crespi of Simon Fraser University in British Columbia and Kyle Summers of East Carolina University argue that these genes are part of an evolutionary struggle between children and their mothers.

Natural selection favors genes that allow children to draw as much nourishment from their mothers as possible. A fetus produces the placenta, which grows aggressively into the mother's tissue and extracts nutrients. That demand puts the fetus in conflict with its mother. Natural selection also favors genes that allow mothers to give birth to healthy children. If a mother sacrifices too much in the pregnancy of one child, she may be less likely to have healthy children afterward. So mothers produce compounds that slow down the flow of nutrients into the fetus.

Each time mothers evolve new strategies to restrain their fetuses, natural selection favors mutations that allow the fetuses to overcome those strategies. "It's a restrained conflict. There's a tug-of-war about how much the fetus is going to take from the mother," Crespi says.

Genes that allow cells to build a better placenta, Crespi and Summers argue, can get hijacked by cancer cells—turned on when they would normally be silent. The ability to stimulate new blood vessel formation and aggressive growth serves a tumor just as it does a placenta. "It's something naturally liable to be co-opted by cancer cell lineages," Summers says. "It sets up the opportunity for mutations to create tools for cancer cells to use to take over the body."

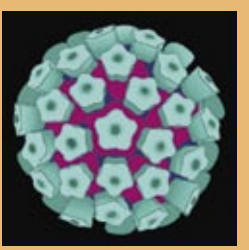
Yet even though activation of these usually quiet genes may make cancers more potent, natural selection may still have favored them because they helped fetuses grow. "You may get selection for a gene variant that helps the fetus get a little more from mom," Crespi says. "But then, when that kid is 60, it might increase the odds of cancer by a few percent. It's still going to be selected for because of the strong positive early effects."

Sperm are another kind of cell that multiplies rapidly. But whereas placental cells proliferate for a few months, sperm-making cells function for a lifetime. "For decades, human males are producing an enormous amount of sperm all the time," says Andrew Simpson of the Ludwig Institute for Cancer Research in New York City. Genes that operate specifically in such cells are also among the fastest evolving in the human genome. A gene that allows a progenitor sperm cell to divide faster than other cells will become more common in a man's population of sperm. That means it will be more likely to get into a fertilized egg and be passed down to future generations.

Evolution of a Cancer-Causing Virus

The American Cancer Society estimates that 17 percent of all cancer cases—more than 1.8 million a year—are caused by viruses and other infectious agents. Scientists are studying the evolution of these cancer-causing pathogens to find hints for fighting them. One such pathogen is the human papillomavirus, responsible for most of the half a million cases of cervical cancer diagnosed annually. The virus can cause host cells to divide long after normal cells would stop and also prevents them from repairing mutations to their DNA.

Scientists have reconstructed some of the virus's evolutionary history by sequencing and comparing the genomes of hundreds of different types of viruses. Papillomaviruses, which form a large family, are found in most vertebrates, in whom they typically engender only warts and other benign growths. Yet when *Homo sapiens* first emerged—about 200,000 years ago in Africa—our ancestors already carried a number of strains that could infect our species and no other animal, and these included cancer-causing types.



HUMAN PAPILLOMAVIRUS is shown in a computer-generated rendering.

After about 100,000 years, *H. sapiens* expanded out of Africa to other continents, bringing the viruses with them. As human populations became isolated from one another, their papillomaviruses did as well. Consequently, the genealogy of human papillomaviruses reflects human genealogy. The oldest lineage of the viruses is most common in living Africans, for example. Native Americans descended from Asians, and their viruses share that kinship.

This coevolution may be medically relevant, because the viruses appear to have adapted to their hosts. In August 2006 scientists published a report in the *Journal of the National Cancer Institute* on the persistence of various virus types in different ethnic groups. A woman who becomes infected by a virus having an ancient association with her ethnic group will carry the virus for a longer time than if she were infected by another type.

Scientists are also investigating how certain benign papillomaviruses evolved to cause cancer. Their discoveries will become all the more important as vaccines are introduced against the viruses. The FDA has approved a vaccine against the most dangerous human papillomavirus strain, known as H16. But evolutionary studies indicate that on rare occasions, human papillomavirus types have traded genes involved in triggering cancer. The global HIV epidemic might raise the risk of this gene swapping. As HIV weakens a person's immune system, more types of human papillomaviruses can invade and coexist. This mingling could conceivably give rise to a new cancer-causing strain for which today's vaccines would be less protective. —*C.Z.*

LINDA M. STANNARD *University of Cape Town/Photo Researchers, Inc.*

Unfortunately for us, genes that make for fast-breeding sperm cells can make for fast-breeding cancer cells. Normally, nonsperm cells prevent these genes from making proteins. "These are genes that need to be firmly silenced, because they are dangerous genes," Simpson says. It appears that in cancer cells, mutations can unlock these sperm genes, allowing the cells to multiply quickly.

How vs. Why

EVOLUTIONARY BIOLOGISTS hope that their research can help in the fight against cancer. In addition to clarifying why evolution has not eradicated cancer, evolutionary biology may shed light on one of the most daunting challenges faced by oncologists: the emergence of drug-resistant tumors.

Chemotherapy drugs often lose their effectiveness against cancer cells. The process has many parallels to the evolution of resistance to antiviral drugs in HIV. Mutations that allow cancer cells to survive exposure to chemotherapy drugs enable the tumor cells to outcompete more vulnerable cells. Understanding the evolution of HIV and other pathogens has helped scientists to come up with new strategies for avoiding resistance. Now scientists are investigating how understanding the evolution within tumors could lead to better ways of using chemotherapy.

The concepts evolutionary biologists have been exploring are relatively new for most cancer biologists. Some are reacting with great enthusiasm. Simpson believes, for instance, that deciphering the rapid evolution of sperm-related genes could help in the fight against tumors that borrow them. "I think it's absolutely crucial to understand exactly why there is such strong selection on these genes," Simpson says. "Understanding that will give us a real insight into cancer."

Bert Vogelstein of the Howard Hughes Medical Institute also finds it useful to view cancer through an evolutionary lens. "Thinking about cancer in evolutionary terms jibes perfectly with the views of cancer molecular geneticists," he says. "In one sense, cancer is a side effect of evolution."

But Vogelstein is not yet persuaded by the significance of fast-evolving cancer genes. "One has to be a little cautious. The first question I would ask is, Are they looking at the whole genome in a wholly unbiased way?" McInerney acknowledges that such systematic studies have not yet been conducted, but the early results have prompted him and other scientists to begin them.

Some cancer specialists are leery of the entire approach. Christopher Benz of the Buck Institute for Age Research says that any insights from evolution should not be accepted until they are put to an experimental test the way any other hypothesis would be. "Call me skeptical," he says.

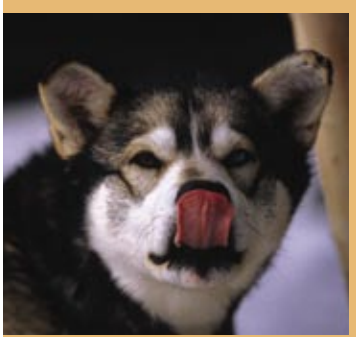
Crespi is familiar with this skepticism, and he thinks that it may emerge from the different kinds of questions evolutionary biologists and cancer biologists ask. "The peo-

DANIEL BOSCHUNG *zefa/Corbis*

The Surprising History of a Dog Cancer

A canine cancer called Sticker's sarcoma can be transmitted both through sex and by licking or touching a tumor. Once established in a new host, it can produce tumors that grow to the size of grapefruits before gradually disappearing. Many scientists once thought that the disease, like cervical cancer, was spread by viruses. Now they know that the cancer cells themselves move from dog to dog and have been spreading this way for centuries.

A team of scientists from University College London and the University of Chicago recently analyzed the genes of Sticker's sarcoma cells collected from dogs around the world. They found that the tumors are much more genetically similar to one another than they are to the dogs in which they grew. Additional research confirmed that the tumors belong to a single lineage of cancer cells.

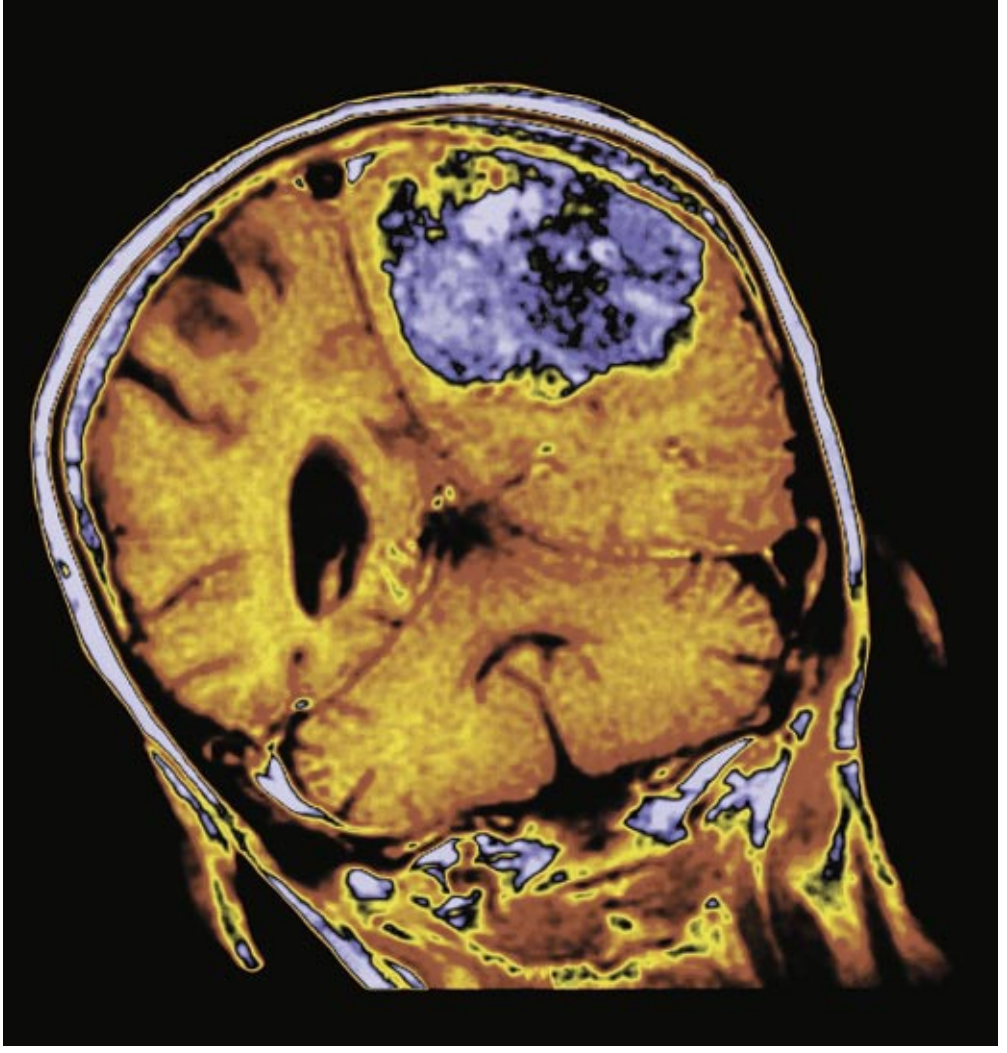


SOME HUSKY might have started the spread of Sticker's sarcoma cells among dogs hundreds of years ago.

"It represents the evolution of a cancer cell into a successful parasite of worldwide distribution," the scientists wrote last year in the journal *Cell*.

Investigators have identified only a few other possible examples of parasitic cancer. Tasmanian devils, for example, can spread a facial tumor by biting one another. Why aren't there more parasitic cancers? Organ transplantation may offer a clue. One of the biggest dangers in organ transplantation is rejection, in which a patient's immune system violently attacks the organ. All vertebrates reject grafts of foreign tissue with this kind of ferocity. It is possible that this rejection response evolved hundreds of millions of years ago as a defense against parasitic cancers.

Sticker's sarcoma appears to have evolved its way around this ancient defense. The cells in the tumor make very few of the surface proteins that vertebrates use to distinguish self from nonself—allowing them to evade an all-out attack from the dog's immune system. Instead the immune system erodes the tumor slowly over the course of several months, and individual cancer cells can survive even after the tumor is gone. Rather than being just an ordinary cancer that dies with its host, it has become a cancer that can live for centuries. —*C.Z.*



Large brain tumor, highlighted in blue

ple working on cancer are working on the how question, and the evolution people are working on the why," he says.

Perhaps by asking different questions, evolutionary biologists will be able to contribute to some of the debates among cancer biologists. One long-standing argument focuses on whether mice are good models for cancer in humans. Some evolutionary biologists argue that they are not, because of their separate history. Rodents inherited the same set of genes as we did from our common ancestor some 100 million years ago, but then many of those genes underwent more change in the two lineages. Cancer-related genes such as FAS may have experienced intense evolutionary change in humans in just the past few million years, making them significantly different from their counterparts in mice.

Mice may also be a poor choice for a cancer model because of the way they reproduce. Scientists have bred lab mice to produce more pups at a faster rate than their wild cousins. Such manipulation may have altered the evolutionary trade-off faced by mice, so that they are rewarded for investing energy into growing quickly and reproducing young. At the same time, this artificial selection may be selecting against cancer defenses. "We have changed their life histories by selecting on their timing of reproduction," Crespi says.

Ultimately, the study of the evolution of cancer may reveal why eradicating the disease has proved so difficult. "There is no real solution to the problem," Breivik says. "Cancer is a fundamental consequence of the way we are made. We are temporary colonies made by our genes to propagate them to the next generation. The ultimate solution to cancer is that we would have to start reproducing ourselves in a different way." SA

ULTIMATELY, STUDY OF THE EVOLUTION OF CANCER MAY REVEAL WHY ERADICATING THE DISEASE HAS PROVED SO DIFFICULT.

MORE TO EXPLORE

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SIMON FRASER/RNC, NEWCASTLE UPON TYNE *Photo Researchers, Inc.*