Sunlight and Skin Cancer

Although most skin cancers appear in older people, the damage often begins decades earlier, when the sun's rays mutate a key gene in a single cell

by David J. Leffell and Douglas E. Brash

In 1775 the British physician Percivall Pott reported a curious prevalence of ragged sores on the scrotums of many chimney sweeps in London. Other doctors might have concluded that the men were afflicted with a venereal disease that was then rampant throughout the city. But Pott was more astute. He realized they were in fact suffering from a type of skin cancer. Pott's discovery was a medical milestone. By observing that men continually exposed to coal tar were "peculiarly liable" to this form of cancer, he documented for the first time that cancer could be caused by an external agent rather than by internal factors.

More recently, investigators have identified another link between the environment and skin cancer, but this time the agent is much more ubiquitous. It is nothing less than light from the sun. The painstaking efforts of dozens of researchers have revealed a great deal about how solar rays contribute to the development of an astonishingly high number of skin cancers every year.

In the U.S. alone, about a million new cases occur annually, rivaling the incidence of all other types of cancer combined. Skin cancer typically takes one of three forms corresponding to the three major types of skin cells: basal cells, squamous cells and melanocytes. Cancer of melanocytes, called malignant melanoma, is the most lethal variety—and perhaps the most mysterious to researchers attempting to understand how these tumors are triggered. Fortunately, it is also the least common. In the U.S. there will be about 38,000 new cases of melanoma this year and approximately 7,000 deaths from the disease. The two other forms, together called nonmelanoma skin cancer, account for the balance of the cases but kill a much smaller percentage of the affected population.

If caught early, most cases of nonmelanoma skin cancer are easily treated in a doctor's office under local anesthesia. Such cancers can be cured by a variety of simple techniques, including scraping, burning, freezing or surgically excising the malignant tissue. Even melanoma, if diagnosed when the tumor is still less than one millimeter thick, can usually be cured by simple excision. But because skin cancer plagues members of all age groups, and because it can become disfiguring and deadly if left untreated, medical researchers have mounted an immense scientific effort over the years to unravel the mechanisms that cause this disease. Curiously, an accident of history contributed much to that quest.

An Accidental Experiment

At the time Pott was studying scrotal cancer, Georgian England had a legal system that inflicted severe punishments for petty crimes: forgery or thievery often resulted in a death sentence. But a backlash against the harshness of execution for such misdemeanors soon led to milder sentences—and thus to the overcrowding of jails. To unburden the country's prisons, the House of Commons voted to banish criminals to remote locales beginning in the 1780s. The destination of choice was a little known shore bordering the South Pacific Ocean. Within a few decades, the east coast of Australia was populated with British and Irish men and women. Those early colonists often shared the Celtic features of fair skin and light hair, and today their descendants predominate on that southern continent.

HUMAN SKIN includes three major cell types, all of which are susceptible to sun-light-induced cancer. Near the base of the epidermis lie round, basal cells. Closer to the surface are flattened, squamous cells. Melanocytes (cells that produce the protective pigment melanin) are interspersed in the basal layer and have numerous extensions that reach outward. Solar rays, which can penetrate well below the surface of the skin, damage segments of a cell's DNA that are particularly vulnerable to ultraviolet light. Damage to a gene called p53 appears crucial to basal cell and squamous cell skin cancers.
What began as an 18th-century attempt at penal reform ultimately culminated in a de facto large-scale experiment on the links between complexion, solar radiation and skin cancer. With their fair skin continually exposed to intense sun, whites in Australia now have the highest rate of all kinds of skin cancer of any people in the world. Their British relatives, who live under cloudy northern skies, are more fortunate. They have a relatively low risk of acquiring cancers of the skin. Aborigines, who with much darker skin are rarely affected by sun-induced malignancies—as do Australian Aborigines, who with much darker skin are rarely affected by sun-induced cancers of the skin.

Investigators recognized as early as 50 years ago that the Australian experience implicated strong sun and fair skin as important risk factors for skin cancer. But for decades scientists were unable to explain what the sun was actually doing to skin cells to make them become cancerous. Clarifying that mystery required more than an accidental experiment on a sun-drenched continent. It took years of study in research laboratories of molecular biologists around the world before the details of that process began to be uncovered.

When the two of us started to attack this problem in the late 1980s, two types of insults from the sun seemed equally suspect. In one category were mutations of specific genes within skin cells. A cell may reproduce excessively if a mutation either turns a normal gene into an overzealous growth promoter (an oncogene) or inactivates a gene that normally limits cell growth (a tumor suppressor gene). The other class of causes we considered at the outset included more widespread events—ones that would affect every sun-exposed cell. For example, the sun’s radiation might suppress the skin’s immune response (reducing its natural ability to eliminate tumor cells) or directly stimulate cell division. With such diverse explanations possible, we knew that isolating the causes of skin cancer would not be easy.

But we were guided by the knowledge that the damaging effects of sunlight can occur many years before tumors appear. Such delayed effects were most clearly demonstrated in studies undertaken by Anne Kricker, then at the University of Western Australia, Robin Marks of the
received a critically high dose of sunlight (which rarely occurred before middle age). Widespread events, such as immunosuppression, last for only a few days from one generation of cells to another). After the injurious radiation ceases. But genetic changes persist (being passed from one generation of cells to another). Looking for genetic changes therefore seemed a more promising avenue for our research. So we began a hunt for sunlight-induced mutations that could occur early in life and set the stage for the development of skin cancer much later on.

A Signature Mutation

That search was daunting. The DNA in a human cell contains as many as 100,000 genes, and each gene typically includes thousands of nucleotides (the building blocks of DNA)—only some of which would be likely to bear traces of sun-induced damage. And even if we managed to identify mutations in skin cancer samples, how could we be sure that sunlight had caused them? Fortunately, other investigators had given us a useful clue by finding that ultraviolet radiation—long suspected to be the carcinogenic factor in sunlight—had a characteristic signature.

After studying everything from viruses to human cells, groups of researchers from Switzerland, France, Canada and the U.S. had shown that ultraviolet light causes mutations at points on a DNA strand containing specific nucleotide bases. Bases are the variable parts of nucleotides and go by the names adenine (A), guanine (G), cytosine (C) and thymine (T). Ultraviolet light creates mutations where a so-called pyrimidine base—cytosine or thymine—lies adjacent to another pyrimidine. About two thirds of these mutations are C-to-T substitutions, and about 10 percent of these changes occur at two adjacent Cs, with both bases changing to Ts. These features of the mutations created by ultraviolet light constitute a fingerprint of sorts, because they are made by no other agents. We thus had a good idea of the kinds of distinctive mutations that should result from exposure to sunlight. But we needed to pinpoint which of the vast number of human genes mutated to produce a carcinogenic effect. Our best guess was that the solution lay with the handful of human genes already known to be involved in cancer.

Of the recognized oncogenes and tumor suppressor genes, we chose to examine a tumor suppressor gene called p53, which is now known to be mutated in more than half of all people’s cancers. At the time, we suspected that p53 might be involved in many cases of skin cancer because of an intriguing connection between nonmelanoma skin cancer and a rare affliction (epidermodysplasia verruciformis) that causes wartlike growths to appear on the skin.

Previous research had revealed that such growths contain DNA from the human papillomavirus and that when these growths are located on sun-exposed skin, they can progress to basal cell or squamous cell cancer. Peter M. Howley and his colleagues at the National Cancer Institute had further shown that one of the proteins made by the papillomavirus inactivates the p53 protein. (Genes give rise to proteins, and the p53 protein, as might be expected, is the product of the p53 gene.) So all indications were that p53 might play a special role in nonmelanoma skin cancer. But we needed solid confirmation.

To find that proof, we studied squamous cell carcinomas, tumors unquestionably linked to sunlight (they occur on the face and hands, especially among whites living in the tropics). In collaboration with Jan Pontén of Uppsala University Hospital in Sweden, we discovered that more than 90 percent of the squamous cell carcinomas from a set of samples collected in the U.S. had a mutation somewhere in the p53 tumor suppressor gene. These mutations occurred at sites with adjacent pyrimidine bases, and they had the distinctive C-to-T pattern associated with ultraviolet exposure. Our research group, along with several others, later pinpointed sunlight-related p53 mutations in basal cell carcinomas as well. (Melanoma does not appear to be associated with alterations to p53. Researchers are still studying cancerous melanocytes for genes affected by sunlight.) After examining samples in our laboratory, Annemarie Ziegler found that precancerous skin also contains mutations of p53, indicating that the genetic changes occur long before repair. If sunlight later burns unaltered cells (c), massively damaged cells will commit “cellular suicide” and be replaced by cells derived from healthy skin nearby (d). But if sunlight burns tissue near a p53-mutated cell that cannot self-destruct (e), the mutated cell may replace the dying, sunburned cells with its own progeny (f), thereby promoting growth of a tumor.
tumors appear. But were these mutations truly the cause of nonmelanoma skin cancer, or were they simply an irrelevant indicator of lifetime exposure to sunlight?

We could rule out this last possibility by the particular way the genetic code had been altered. The nucleotides in genes are arranged in well-defined codons—groups of three bases that specify different amino acids. The sequence of codons in a gene determines the sequence of amino acids that are strung together to construct a protein. But different codons can sometimes specify the same amino acid—as if the name of the amino acid could be spelled any of several ways. Typically the amino acid does not change when the first two bases of the codon are constant and only the third varies. Hence, if the \( p53 \) mutations found in skin cancer were just a random effect of exposure to the sun, we would expect to find changes in the third position occurring as often as in the first or second. That is, there would be plenty of examples where the codon mutated (underwent a nucleotide base substitution) without altering its corresponding amino acid. Yet studies of this gene in skin cancers from around the globe had consistently revealed mutations that modified one or more amino acids in the \( p53 \) protein. These genetic changes to \( p53 \), then, were not just a side effect of ultraviolet exposure. They were in fact causing the skin cancers.

To better understand how the \( p53 \) gene was affected in nonmelanoma skin cancer, we investigated whether certain segments of the \( p53 \) gene were particularly prone to the mutation by sunlight of adjacent pyrimidine bases (that is, \( C \)s or \( T \)s). Biologists have found so-called mutation hot spots (places on a DNA strand where mutations tend to occur) whenever they expose living cells to carcinogens. After analyzing many tumors, we determined that the \( p53 \) gene in nonmelanoma skin cancer contains about nine hot spots. In cancers unrelated to sunlight (such as colon or bladder cancer), five codons of \( p53 \) are most often mutated, three of which are among the hot spots in skin cancers. At the two hot spots found only in the other cancers, the mutating \( C \) is flanked on either side by a \( G \) or \( A \) but never by a \( T \) or another \( C \). Lacking a pair of pyrimidine bases, equivalent sites on the DNA of skin cells are protected from mutation by ultraviolet light.

Of the hundreds of places on the \( p53 \) gene with adjacent pyrimidines, why do only a few sites act as hot spots when cells are exposed to sunlight? Several researchers have recently helped answer that question by building on a discovery made more than three decades ago at Oak Ridge National Laboratory by Richard B. Setlow and William L. Carrier. Setlow and Carrier determined that cells can reverse ultraviolet damage to their DNA by an enzymatic process called excision repair. Cells essentially snip out disrupted bases and replace them with intact ones. Working in our lab in 1992, Subrahmanyam Kunala showed that cells repair damage particularly slowly at some pyrimidine pairs. Subsequently, Gerd P. Pfeifer and his colleagues at the City of Hope Beckman Research Institute in Duarte, Calif., found that cells repair the \( p53 \) sites mutated in nonmelanoma skin cancer more sluggishly than they do many other sites in the gene. Hence, it seems quite likely that the hot spots we found for skin cancer owe their existence to an inability of skin cells to mend these sites efficiently.

Cellular Proofreading

Even after we had identified the relevant \( p53 \) mutations, the story of carcinogenesis remained woefully incomplete. After all, genes do not get cancer—cells do. It was clear enough that the \( p53 \) protein must operate in normal...
sunlight can grow. By inducing healthy cells to kill themselves off, sunlight favors the proliferation of p53-mutated cells. In effect, sunlight acts twice to cause cancer: once to mutate the p53 gene and then afterward to set up conditions for the unrestrained growth of the altered cell line. These two actions, mutation and tumor promotion, are the one-two blows of carcinogenesis. Although mutation and promotion are carried out by separate agents in other tumors, in skin cancer ultraviolet radiation appears to throw both punches.

There are undoubtedly other genes involved in the development of skin cancer as well as other effects of sunlight that researchers do not yet fully understand. For example, medical researchers know that Gorlin syndrome (a disease in which patients have multiple basal cell cancers) is caused by an inherited mutation in a different tumor suppressor gene. With further investigation, the various mechanisms of carcinogenesis will become even more clear, and scientists may find clever ways to interrupt the progression of normal skin cells to cancerous ones.

It is not beyond reason to hope that the detailed understanding researchers are gaining of nonmelanoma skin cancer will yield new kinds of therapies. Perhaps drugs that restore normal function to a mutated p53 protein will allow doctors to offer their patients an effective remedy that does not involve surgery. Such a cure, perhaps administered as a simple skin cream that is absorbed by the affected cells, might be available within the next decade or two. If so, it will be of great benefit to countless aging members of the sun-loving baby-boom generation—a group to which we both admittedly belong.

The Authors

DAVID J. LEFFELL and DOUGLAS E. BRASH have worked together for nearly a decade to understand the role of the sun in causing skin cancer. Leffell, a professor of dermatology and surgery at the Yale School of Medicine, has brought to their research collaboration the experience gained in clinical practice. He earned his M.D. at McGill University in 1981 and trained at Cornell Medical School, Memorial Sloan-Kettering Cancer Center and the University of Michigan before taking a position on the faculty at Yale in 1988. Brash, too, is on the medical school faculty at Yale, and his credentials include a bachelor's degree in engineering physics from the University of Illinois. He shifted from engineering to the study of biophysics at Ohio State University, where he received his Ph.D. in 1979. Thereafter Brash pursued postdoctoral training in microbiology (at the Harvard School of Public Health) and pathology (at Harvard Medical School) until 1984. He spent the next five years at the National Cancer Institute before moving to Yale.

Further Reading


