More often than not, cancer appears hand in hand with old age. Cancer is wedded to the progression of time through its need to accumulate multiple mutations. But some studies suggest a potentially deeper relation in which aging supplies cancer with a unique terrain where it can thrive. Although unresolved questions abound about the relation between cancer and aging, basic scientific insights are emerging, as are new ideas for keeping the lethal disease at bay.

Introduction
Among those who tread the final stretch of cancer’s deadly path, old people vastly outnumber young people. Octogenarians are approximately 1000 times more likely to die from cancer than are people in their 20s, according to Richard Peto of the University of Oxford, U.K. In general, the ratio of two people’s ages raised to the fifth power provides a rough indicator of their relative risk of dying of cancer.

No one knows exactly what underlying processes forge the link between cancer and old age (Fig. 1), but researchers have a number of ideas. Normal cells descend into cancer in multiple steps, each of which takes time (1). Like the Darwinian evolution of species, tumor development is powered by the selection of advantageous mutations, which collaborate to make cancerous cells grow better than their peers. Many cancer cells possess, for example, damaged versions of genes that normally put the brakes on inappropriate cell division. “I would say the simplest and most compelling explanation for why cancer is an age-dependent phenomenon derives from the need to have a multiply mutated cell,” says Robert Weinberg of the Massachusetts Institute of Technology.

But whether time alone couples cancer to aging is debatable. Supporters of a deeper relation note, for example, that both short- and long-lived organisms often develop cancer toward the ends of their lives. This observation implies that cancer’s development is linked to physiological age rather than simply to the passage of absolute time. Furthermore, aging shapes host tissues in a manner that could nurture cancer’s birth and maturation, according to some studies.

Perhaps the most dreaded hallmark of aging is that our time of death is drawing near. Studying cancer, a leading cause of death in old age, promises to help illuminate the mechanisms that underlie this vulnerability and could lead to the development of treatments that increase life expectancy.

Impediments to Cancer
Considering the hurdles a cell has to clear on its way to malignancy, it’s not surprising that cancer takes time to develop (2) (Fig. 2). Normal cells require four to seven genetic hits to turn into invasive cancer cells (3). Even after cells start to go bad, limited supplies of growth activators and the presence of growth inhibitors in most tissues hinder the progression. And death is always lurking for abnormal cells; some mutations that might otherwise lubricate the slide into cancer instead trigger an alarm that spurs cell suicide (2).

Then there’s the telomere roadblock. Telomeres are structures that cap the ends of chromosomes and operate as fuses to cellular life. Most human cells can divide only a few dozen times in a culture dish before their telomeres erode and proliferation freezes. Although the connection between these events in culture and cell death in intact organisms is unclear (see “More Than a Sum of Our Cells”), some studies suggest that a similar process could block the growth of aspiring cancer cells. Finally, nutrients and space limit tumor growth. To threaten an organism’s life, tumors must stimulate the growth of new blood vessels and spread to additional sites in the body.
So how do cancer cells collect the alterations they require to overcome these formidable barriers? “I would estimate that, if you subtract smoking, more than half of cancer deaths are caused by endogenous mutagenic agents—those generated within cells,” says Lawrence Loeb of the University of Washington, Seattle.

Among these agents, reactive oxygen species, byproducts of normal metabolism, rank high in their destructive potential (4) (see “The Two Faces of Oxygen†”). Oxidative reactions batter the DNA in each cell of a normal human with about 10,000 lesions per day, according to Bruce Ames of the University of California, Berkeley, and several studies have suggested that oxidative stress correlates with both cancer and aging. For example, the incidence rate for most types of cancers seems to be approximately twofold greater in the quarter of the population that eats the least amount of fruits and vegetables, which are rich in antioxidants, compared to the quarter that eats the most fruits and vegetables (5).

Despite the thousands of hits delivered daily by oxidative reactions and other insults, only a tiny fraction alter gene function directly (6). DNA repair enzymes continuously fix damaged DNA. And because genes compose less than 2% of the genome, most random hits fall on gene-free stretches of DNA. A more significant source of cancer-causing damage may stem from errors during DNA repair, particularly because some of these mistakes can lead to large chromosomal alterations, some researchers argue. “In one stroke you can influence many, many genes,” says Jan Vijg of the University of Texas, San Antonio.

Indeed, several genetic diseases that predispose people to developing cancer involve mutations in DNA repair genes. And some of these diseases are associated with premature aging. For example, people who carry a defective form of the Werner helicase, an enzyme involved in DNA repair and other DNA functions, suffer from many symptoms of accelerated aging, including an increased risk of developing cancer (7).

Mutation frequency rises with age in both humans and mice (6) (Fig. 3). Estimates of average mutation rates from studies of cells in a dish don’t seem to account for those required by cancer cells in an animal (8). But Vijg argues that this rate “is not the real mutation rate as it takes place in vivo.” Some studies that have tracked the accumulation of mutations in mice carrying marker genes, for example, suggest that spontaneous mutation rates may be high enough to fulfill many of cancer’s mutational needs (6). Yet Vijg acknowledges that mutations in cancer cells are so numerous that other factors almost certainly contribute. In addition, the genetic alterations are varied and extreme, suggesting that something more sinister than random mutation is at work. Most

†sageke.sciencemag.org/cgi/content/full/sageke;2001/1/oa5

Fig. 2: Vaulting to malignancy. Cells must clear multiple hurdles such as the ones shown above to become cancerous.

Fig. 3: Accrued damage. Mutations accumulate over time—but at different rates—in a variety of mouse tissues.
cancers of old age sport altered numbers of chromosomes, abnormal fusions of chromosome fragments, and amplified genes (9). “Cancer cells are a mess, an absolute mess,” says Judith Campisi of Lawrence Berkeley National Laboratory (LBNL) in California.

One way in which cancer cells might turn into such a shambles is by acquiring defects in genes that normally guarantee the fidelity of DNA synthesis or the effectiveness of DNA repair (10). An alteration in one of these genes can spawn many more mutations and create what Loeb calls a “mutator phenotype” (Fig. 4). Although some researchers remain skeptical (11), many believe that mutator phenotypes help drive cancer, particularly because recent studies indicate that they appear early in tumor development (12).

**Telomeres and Crisis**

One mutator phenotype has recently stepped into the limelight: telomere dysfunction (13). The key evidence that placed it on stage came from studies performed by Ron DePinho of the Dana-Farber Cancer Institute in Boston and Carol Greider of Johns Hopkins University in Baltimore (14-16). The studies shed light on how the formation of tumors in mice differs from that in humans. Cancer strikes different tissues in aging mice and humans: Mice tend to get cancers of the lymphatic system that in humans. Cancer strikes different tissues in aging mice and humans: Mice tend to get cancers of the lymphatic system, whereas humans tend to get epithelial cancers, such as colon and breast cancer. Seeking an underlying cause for this difference, the researchers zeroed in on telomeres.

The telomeres of a typical human cell growing in a dish shrink with each cell division. Abnormally short telomeres can trigger chromosomes to fuse and fracture; a cell in this state is in “crisis.” In healthy cells, genome caretakers such as the tumor suppressor molecule p53 shut down cell division well before telomeres reach this length. But if these caretakers are inactive—say, by a mutation—as often occurs in human tumors, cells continue to divide and enter crisis.

Mouse cells, however, are different. “Aspiring cancer cells in the mouse do not experience crisis,” says DePinho. Mouse telomeres don’t erode, because mouse cells produce telomerase, an enzyme that maintains telomere length. When DePinho and colleagues generated mice that mimic two critical aspects of human cancer biology—lack of telomerase production and defective p53—they witnessed the development of humanlike tumors (15).

On the basis of these findings, DePinho suggests the following scenario: Would-be cancer cells that carry both eroded telomeres and a mutation in p53 enter crisis, which results in chromosome breaks and fusions. This process allows those cells to “reshuffle their genetic decks, generating wholesale gains and losses throughout the genome,” he says. “Rare cells will then emerge that have a pro-cancer profile of genetic alterations.” Indeed, Nicholas Hastie of the Medical Research Council in Edinburgh, U.K. (17), and Titia de Lange at Rockefeller University in New York City (18) previously proposed that loss of telomeres might contribute to genome instability in cancer.

Thanks to the reshuffling, postulates DePinho, a few cells acquire mutations that enable them to overcome some of cancer’s barriers—by gaining independence from growth factors or insensitivity to growth inhibitors, for example. And in some of these cells, telomerase expression is also activated, which allows them to divide indefinitely.

But why are epithelial cells more likely to travel this route than are others, such as the lymphoid cells that tend to turn cancerous in mice? Perhaps the undifferentiated cells—stem cells—that give rise to epithelial cells are particularly prone to telomere-based genetic instability because they divide frequently. Doubling shrinks telomeres, and it also increases cell numbers, providing more potential targets for mutation. In addition, DePinho notes that epithelial cells appear less sensitive to telomere dysfunction than do other cells that divide frequently. Lymphoid cells, for example, are more likely to die when their telomeres get short.

Of particular interest is how telomere length, telomerase activity, and genetic instability change during tumor progression in animals: Is telomerase activity low in the early stages of tumor progression to trigger crisis, but high at later stages to ensure growth? Recent observations from DePinho’s team indicate that, as predicted by his model, human colon cells on their way to malignancy contain dysfunctional telomeres and display chromosomal instability (16). But Jerry Shay of the University of Texas Southwestern Medical Center (UT Southwestern) in Dallas says that a causal link has yet to be established. “There is no direct evidence that you need telomere shortening to make cancer,” he says.

David Wynford-Thomas of the University of Wales in Cardiff thinks that to obtain a full picture of the situation researchers will need to monitor telomerase activity during tumor progression. Shay and his colleagues have found that almost all types of malignant cells express telomerase (19, 20). But obtaining reliable measures of the enzyme’s activity in situ has been very difficult. “The key will be to get better tools,” says Wynford-Thomas.
DNA Methylation

Processes in addition to mutation, such as aberrant methylations of cytosines in DNA, promote cancer by altering gene function (21). Some studies suggest that these abnormalities accumulate with age, as do mutations.

Methylation in transcriptional regulatory sequences can block, or silence, the activities of genes. Several cancers seem to benefit from this process: Tumor suppressor genes are silenced by methylation in an ever-lengthening list of tumors. And several studies indicate that methylations also crop up in normal tissues as they age (22). Jean-Pierre Issa of the University of Texas M. D. Anderson Cancer Center in Houston recently found that 72% of the aberrant methylations in a colon cancer cell line were also present in normal colon cells of aged individuals (23). “We think that age-related methylation silences genes and changes the cells’ physiology, and this is what then predisposes them to cancer,” he says.

But Issa cautions that the causal links in his hypothesis remain unproven. “Age-related methylation happens,” he says. “But the idea that it actually contributes to cancer formation is a hypothesis.” In support of that scenario, a study in 1995 showed that mice bearing a mutation that predisposes them to colon cancer develop fewer tumors when they also harbor a mutation in an enzyme that methylates DNA (24).

The few regulatory sequences that carry age-related methylations associated with cancer, however, represent only a small fraction of the complete genome. Some cancerous and old cells appear to be undermethylated (25, 26). When cells age, they seem to gain a few methylations in key regulatory sequences but lose them elsewhere, says Issa. Either or both of these processes could lead to cancer, but they also could simply accompany it. “In the methylation field, there appears to be little attempt to distinguish consequence from cause;” says Timothy Bestor of Columbia University in New York City. “What we need is to put forward testable hypotheses.”

Bestor has started to do so by unifying several disparate observations. In 1998, Rudolf Jaenisch of the Massachusetts Institute of Technology in Cambridge showed that mutation rates skyrocket in cells that lack a particular DNA-methylating enzyme (27). He hypothesized that this increased rate could be due, at least partially, to recombination—the breaking and rejoining of DNA fragments. This idea is based in part on the observation that undermethylation often occurs in cells such as the precursors of germ cells that generate genetic variability through recombination. Bestor thinks that the recombination proposed by Jaenisch might occur mostly through transposons, repeated sequences scattered throughout the genome, which some studies have fingered as recombination hotspots and which account for more than 90% of the genome’s cytosine methylations.

And transposons might do more than boost recombination. Bestor has observed that demethylation triggers copious transcription of at least one type of transposon in mice (28). Among the scores of resulting transcripts, some might include bits of the regulatory sequences of neighboring genes, he proposes. Extrapolating from studies in plants, he suggests that RNA copies complementary to critical regulatory regions might silence their corresponding genes by inducing methylation (29). Hypermethylation associated with cancer could be explained, at least in part, by the demethylation of transposons (30). “It’s an attempt to reconcile two contradictory observations: global demethylation in certain cancers with focal hypermethylation,” he says.

A Cancer-Prone Environment?

Aging clearly provides cancer with the precious time it needs to collect multiple DNA alterations. But is absolute time the sole contribution aging makes to cancer? Or does the physiology of aging also lend cancer a helping hand?

The simple passage of time cannot explain why short-lived species, such as mice, develop tumors 6 or 7 decades before their longer lived human cousins do (31), notes Richard Miller of the University of Michigan, Ann Arbor. In addition to the differences in life-span, humans have many more cells that could serve as potential targets for cancer transformation. “It’s a 3000-fold difference [in numbers of cells], so the rate of appearance of cancers ought to be 3000-fold higher, but in fact it’s 30 times lower,” he says.

In addition, results from treatments that enhance longevity, such as a calorie-restricted diet, suggest that many of the changes that accompany aging, including the accumulation of mutations and the development of tumors, lag in parallel (32). And searches for genes that regulate life-span in several organisms have revealed that changes in single genes can affect multiple age-associated processes simultaneously, in some cases including cancer formation (33).

But some investigators take a different viewpoint. Citing experiments in which researchers exposed animals to potent carcinogens, Oxford’s Peto notes that most tumors develop largely as a function of time, not age. And in a few cases, cancers form more rapidly in young animals than in old ones, suggesting that the physiology of aged animals is, if anything, less conducive to tumor formation (34). “In many senses, I think age is not related to cancer,” he says. “I think there isn’t any profound relationship.”

Recent work is exposing age-associated changes that may help sow the seeds of cancer. On the basis of studies in cultured cells, LBNL’s Campisi suggests that tissues of old organisms are peppered with senescent cells, which can’t proliferate or perform their specialized functions properly. In young animals, senescence—at a low level—probably helps fend off cancer by preventing cells with cancer-prone alterations from duplicating. But as organisms age, senescent cells accumulate and can convert a tissue into fertile soil for cancer growth, Campisi proposes.

In young animals, senescence—at a low level—probably helps fend off cancer by preventing cells with cancer-prone alterations from duplicating. But as organisms age, senescent cells accumulate and can convert a tissue into fertile soil for cancer growth, Campisi proposes.
better when seeded onto senescent rather than presenescent fibroblasts. And when injected into mice, senescent fibroblasts foster tumor formation much more frequently than do presenescent fibroblasts. “We asked whether senescent fibroblasts stimulated tumorigenesis,” says Campisi. “And the answer in most cases was clearly yes.”

But aged physiology isn’t always cancer’s ally. “The fact is that tumors grow more slowly in old animals and in old people,” says William Ershler of the Institute for Advanced Studies in Aging and Geriatric Medicine in Washington, D.C. Experiments by him and others suggest that the limited growth results, at least in part, from poor blood flow to the tumor (36).

Campisi offers a potential explanation for these apparently paradoxical observations. “Our results suggest that the senescent environment favors tumorigenesis but not necessarily tumor growth,” she says. “Once a cancer develops to a size where blood supply is [a] limiting [factor], the old host may be a less favorable environment than a young host.”

Aging fibroblasts are not the only cells that could help or hinder cancer’s development. Cells of the immune system also change drastically with age (37). “The immune system of an older person is not a desirable thing to have,” says Miller. “But the question of whether it provides low-quality defenses against spontaneous cancers is controversial.”

The immune system can protect mice against cancer, report Robert Schreiber of Washington University School of Medicine in St. Louis, Missouri, and his colleagues. Lymphocytes and the immune stimulator, interferon γ, cooperate to inhibit the development of tumors (38). In addition, Miller has found that the status of the mouse immune system correlates with longevity (39), and his preliminary results suggest that, in particular, immune status correlates with the risk of dying from cancer. “It could be because immune decline hastens cancer progression, or because immune decline is an index of the aging process,” says Miller.

Perhaps the strongest evidence that the immune system does not play a major role in controlling cancer is the observation that organisms with severe immunodeficiencies don’t face a noticeable increase in risk. “If the immune decline that is part of normal aging is the reason that older people get more cancer, then you’d expect patients with AIDS or patients who are on immunosuppressive therapies to develop the cancers that you see in old people,” says Ershler. “But they don’t.” Although AIDS patients tend to get cancers such as Kaposi’s sarcoma, they do not usually suffer from the types of cancers that afflict the elderly.

Aging also seems to help determine the subcellular terrain in which cancer develops, decreasing its fertility in some cases and perhaps enhancing it in others. Some growth factor receptors—molecules that spur cell division and can foster cancer development—are less likely to increase in cancer as people grow older. For example, breast cancers of young women are more likely to overproduce the ErbB2 receptor than are those of elderly women, according to Christopher Benz of the Buck Institute for Age Research in Novato, California. In contrast, normal and malignant cells of older breast tissue seem to produce much more of the estrogen receptor, a hormone receptor that boosts cell growth by regulating the transcription of several genes, Benz says.

Searching for underlying mechanisms, Benz has obtained preliminary results indicating that the transcription factor Sp1, which appears to cooperate with estrogen receptors to regulate gene expression, tends to lose its ability to bind DNA with age. He suspects that the Sp1 protein accumulates oxidative damage with aging. Oxidative reactions could thus link cancer and aging not only by injuring DNA but also by altering critical proteins.

Looking Ahead

The wealth of proposed links between cancer and aging makes it easy to justify cancer’s predilection for age, although most of these connections rely on correlations rather than proven cause. Evolutionary theory provides clues about how this relation developed (40) (see “Aging Research Grows Up”‡). In any species, the force of natural selection weakens with increasing age. The key to evolutionary success lies in reproduction, so traits that help young animals survive will probably be selected even if they harm older organisms. “You basically stay alive well enough to reproduce,” says Wales’s Wynford-Thomas. “And then after that, all hell can break loose.”

That idea might help explain why cancer tends to afflict rodents when they’re only 2 or 3 years old, whereas it usually takes decades to strike humans. Perhaps evolution has selected mechanisms that protect humans from developing cancers before they’ve had a chance to reproduce. UT Southwestern’s Shay speculates that telomerase repression is one such mechanism (41). Short-lived vertebrates such as mice, he suggests, benefit from keeping telomerase continuously turned on, as it provides them with an unlimited supply of cells to maintain and repair damaged tissue. But longer lived vertebrates may accrue greater benefits from repressing telomerase to protect themselves against cancer in the long term. The proposal is far from proven, however. It remains uncertain, for example, whether the correlation between telomerase repression and longer life-span holds across many species.

By understanding why age so often escorts its hosts down the road to cancer, researchers hope they will succeed in developing therapies to prolong life. The University of Washington’s Loeb, for example, dreams of decreasing mutation rates. It is not unusual for cancer to take 20 years to develop, so a mere twofold reduction in mutations could stave off cancer for decades. Wynford-Thomas, on the other hand, imagines adding artificial checkpoints to limit cell division. And those who view cancer as inextricably tied to the physiology of aging envision treatments that could simultaneously delay both aging and cancer.

Marina Chicurel writes and consults from Santa Cruz, California. To the best of her ability, she steers clear of dangerous liaisons.

Glossary

Epithelial Relating to the tightly packed sheet of cells that lines interior and exterior surfaces in multicellular organisms; epithelial cells, for example, form the skin, the gut lining, the surfaces of mucous membranes, and the lining of ducts and glands.

ErbB2 receptor An overactive mutant form of the receptor that binds to epidermal growth factor (EGF). In its normal form, the EGF receptor plays a part in the development of mammary epithelium; cells with this altered form of the receptor behave as though they are constantly being signaled to proliferate by EGF.

Estrogen receptor A protein that binds to estrogen, a hormone that promotes cell proliferation in the breast and uterine lining and performs important functions in other target tissues such as liver and bone. Drugs that block the binding of estrogen to its receptor (such as tamoxifen) or inhibit estrogen synthesis are widely used to prevent or delay the recurrence of breast cancer.

 Fibroblasts Flattened, irregular-shaped cells ubiquitous in connective tissue; fibroblasts are a type of epithelial cell that can respond to growth factors by increasing their rate of cell division and tissue formation.

‡sageke.sciencemag.org/cgi/content/full/sageke;2001/1/oa1
kidney and lung tumours. The p53 protein appears to suppress tumor growth, both by preventing the proliferation of cells that have sustained DNA damage and by promoting their death. When p53 is mutated, cancer cells can continue to divide even though their DNA is damaged. The p53 protein is considered a tumor suppressor gene because it plays a critical role in preventing the development of cancer.


cytokine molecule stimulates the growth and activity of lymphocytes and other immune system cells. This evidence suggests that p53 is essential for the proper functioning of the immune system.

**References**


