Understanding chronic inflammation, which contributes to heart disease, Alzheimer's and a variety of other ailments, may be a key to unlocking the mysteries of cancer

A Malignant FLA

KEY CONCEPTS

- Until recently, cancer researchers had focused primarily on genetic changes as the underlying cause of the disease.
- In this decade investigators have come to realize that the developing tumor can commandeer the immune system's inflammatory component—normally part of the wound-healing process—to foster carcinogenesis.
- A new generation of anti-inflammatory drugs may join traditional chemotherapies, which could keep solid tumors or premalignancies localized to one place. —*The Editors*

More than 500 million years ago a set of specialized enzymes and proteins evolved to defend our primitive ancestors against assaults from the outside world. If a microbe breached the shell of some Cambrian-era fauna, the members of this early vintage immune system would stage a savage but coordinated attack on these interlopers—punching holes in cell walls, spitting out chemical toxins or simply swallowing and digesting the enemy whole. Once the invaders were dispatched, the immune battalion would start to heal damaged cells, or if the attacked cells were too badly damaged it would put them to rest.

This inflammatory immune response worked so well that many aspects of it have been preserved during the protracted aeons of evolution. We know this to be true because studies have found that we share many of the same immune genes as the lowly fruit fly—and vertebrates and invertebrates diverged from a common ancestor in excess of half a billion years ago.

For years, immunology researchers have paid relatively little attention to this thuggish innate immune system, basically thinking of it as a crew of biochemical bouncers that pummel anything able to penetrate the tiniest opening in a living being's skin or shell. They lavished their attention, instead, on the more advanced adaptive immune system, which can marshal antibodies and other weaponry that identify and then target an intruder with a specificity lacking in the untamed innate system.

In the past 15 years, innate immunity has come into its own. Inflammation, its hallmark characteristic, has gained recognition as an underlying contributor to virtually every chronic disease—a list that, besides obvious culprits such as rheumatoid arthritis and Crohn's disease, includes diabetes and depression, along with major killers such as heart disease and stroke [*see sidebar on page 65*]. The possibility of a link with a third major killer—cancer—has received intensive scrutiny in this decade. "The connection between inflammation and cancer has moved to center stage in the research arena," notes Robert A. Weinberg of the Massachusetts Institute of Technology's Whitehead Institute for Biomedical Research, who has highlighted the changing emphasis in a revision of his leading textbook, *The Biology of Cancer* (Garland Science, 2006).

This transformation recognizes that the immune inflammatory state serves as a key mediator of the middle stages of tumor development. Cancer begins with a series of genetic changes that prompt a group of cells to overreplicate and then invade surrounding tissue, the point at which true malignancy begins. Eventually some tumor cells may break off and establish new

ME

BY GARY STIX

growths (metastases) at distant sites. That much has been understood for a long time. But cancer biologists and immunologists have begun to realize that the progression from diseased tissue to full-blown invasive cancer often requires cells that normally participate in healing cuts and scrapes to be diverted to the environs of the premalignant tissue, where they are hijacked to become co-conspirators that aid and abet carcinogenesis. As some researchers have described the malignant state: genetic damage is the match that lights the fire, and inflammation is the fuel that feeds it.

In this rewriting of the textbooks, a tumor is not just a clump of aberrant cells; it also includes a support system, a tumor microenvironment, which encompasses a multitude of varying immune cell types and crisscrossing chemical signals, along with a network of blood vessels. The tumor assumes the status of an outlaw organ that exists not to pump blood or rid the body of toxins but to serve only its own ends.

This new view implies that rooting out every

TUMOR DEVELOPMENT progresses in some cancers through the effects of what cancer biologists have labeled a "smoldering" inflammation, in which the tumor recruits immune cells that linger in its surroundings and within the malignant mass.

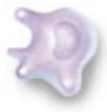
JEFF JOHNSON *Hybrid Medical Animation*

THE PLAYERS

The immune system consists of innate cells, which form a first line of defense against pathogens, and members of the adaptive system, which targets invaders with greater specificity.

INNATE

MACROPHAGE

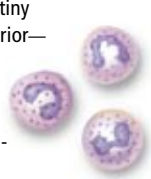


This immune defender engulfs and consumes pathogen invaders.

MAST CELL

This cell releases histamine and other chemicals that promote inflammation.

GRANULOCYTE



Three cell types with tiny granules in their interior—the neutrophil, eosinophil and basophil—participate in the inflammatory response.

DENDRITIC CELL

It presents antigens—fragments of protein or other molecules from pathogens or cancer cells—to adaptive immune cells, inducing the cells to attack bearers of the displayed antigens.

NATURAL KILLER CELL

This cell destroys the body's own cells that have become infected with pathogens; it also goes after cancer cells.

ADAPTIVE

B CELL

Antigens stimulate this cell to divide and produce antibodies that neutralize invaders or tag them for killing.

T CELL

A killer T cell destroys an infected cell in which it detects the presence of antigens. Other T cells—such as helper and regulatory types—coordinate the immune response.

last cancer cell in the body might not be necessary. Anti-inflammatory cancer therapy instead would prevent premalignant cells from turning fully cancerous or would impede an existing tumor from spreading to distant sites in the body. Cancer sufferers might then be able to survive, in the same way that new drugs have let HIV patients live longer. "I don't think a cure is necessarily the goal. It doesn't need to be," comments Lisa M. Coussens, a cancer biologist at the University of California, San Francisco. "If you can manage the disease and live your natural life span, that's a huge win."

Multiple Lines of Defense

Comprehension of the link between inflammation and cancer requires knowing how the body reacts to invaders—and how normal healing is then subverted into promoting cancer when the inflammatory state lasts too long. After you step on a nail, the bacteria that invade the sole of your foot receive a welcome from an array of proteins and white blood cells that resemble rejects from central casting for the movie *Creepshow 2*. Just one example: Some 20 complement proteins, so called because they complement other bodily defense mechanisms, chemically spritz pathogens until the invaders explode into a big protoplasmic mess. While the complement system slimes the area, an assemblage known in immunology textbooks as professional phagocytes—literally "expert eating cells"—goes to work.

Lacking table manners, these Pac-Man-like macrophages and neutrophils proceed to engulf and consume the uninvited guests. Other members of the attack brigade include natural killer cells, mast cells and eosinophils. Healing represents more than launching an offensive against invaders. Blood platelets involved with clotting migrate to the break in the skin from an inner layer infused with blood vessels. Enzymes direct the repair of the extracellular matrix, the protein-based mortar in which the cells are immobilized. A scab forms, the skin grows back and the whole process of inflammation ends. Sometimes, though, inflammation does not stop. Any tissue (not just skin) that is chronically inflamed because of the persistent presence of pathogens, toxins or genetic damage helps to spur illness, from heart disease to cancer.

Beyond this first layer of defense, vertebrates are equipped with additional weaponry. The adaptive system learns an invader's specific molecular signature and then uses it as a target for killing. Among the protagonists are B cells, which produce antibody molecules able to neutralize pathogens or mark them for destruction, and T cells, which prompt infected cells to kill themselves or secrete chemicals that direct the activities of other immune players.

In recent years a body of evidence has accumulated to show that chronic inflammation can play an important role in the progression of some types of tumors from a premalignant state to full-blown disease. A link between cancer and inflammation has long been suspected. In 1863 the prominent German pathologist Rudolf Virchow noted the presence of so-called lymphoreticular infiltrate (white blood cells) in malignant tissue. As early as 1978 Alberto Mantovani of Humanitas Clinical Institute and the University of Milan had observed that innate immune cells tend to congregate around some tumors. Cancer biologist Harold F. Dvorak of Harvard Medical School remarked in 1986 that tumors are "wounds that do not heal." The status quo, though, lay elsewhere. Even a decade ago many biologists still hewed to the idea that the immune system serves not only to eliminate pathogens but to ferret out cells that are the abnormal precursors of cancer. But a closer look at the microenvironment surrounding tumors found the unexpected.

Hunting Pigeons

In the late 1990s Frances Balkwill of the Institute of Cancer at Queen Mary, University of London, had been doing research on a cytokine (a hormonelike immune signaling molecule) known as tumor necrosis factor (TNF), which was named for its ability to kill cancer cells when administered directly into a tumor at high levels. But when TNF lingers as a chronic, low-level presence in the tumor, it acts very differently. Balkwill's lab turned off the TNF gene in mice so that the rodents could not produce the protein: to their surprise, the mice did not contract tumors. "That really put us as the cat among pigeons," she recalls. "All the people who were working on TNF as an anticancer agent were horrified. This cytokine they thought was a treatment for cancer was actually working as an endogenous tumor promoter."

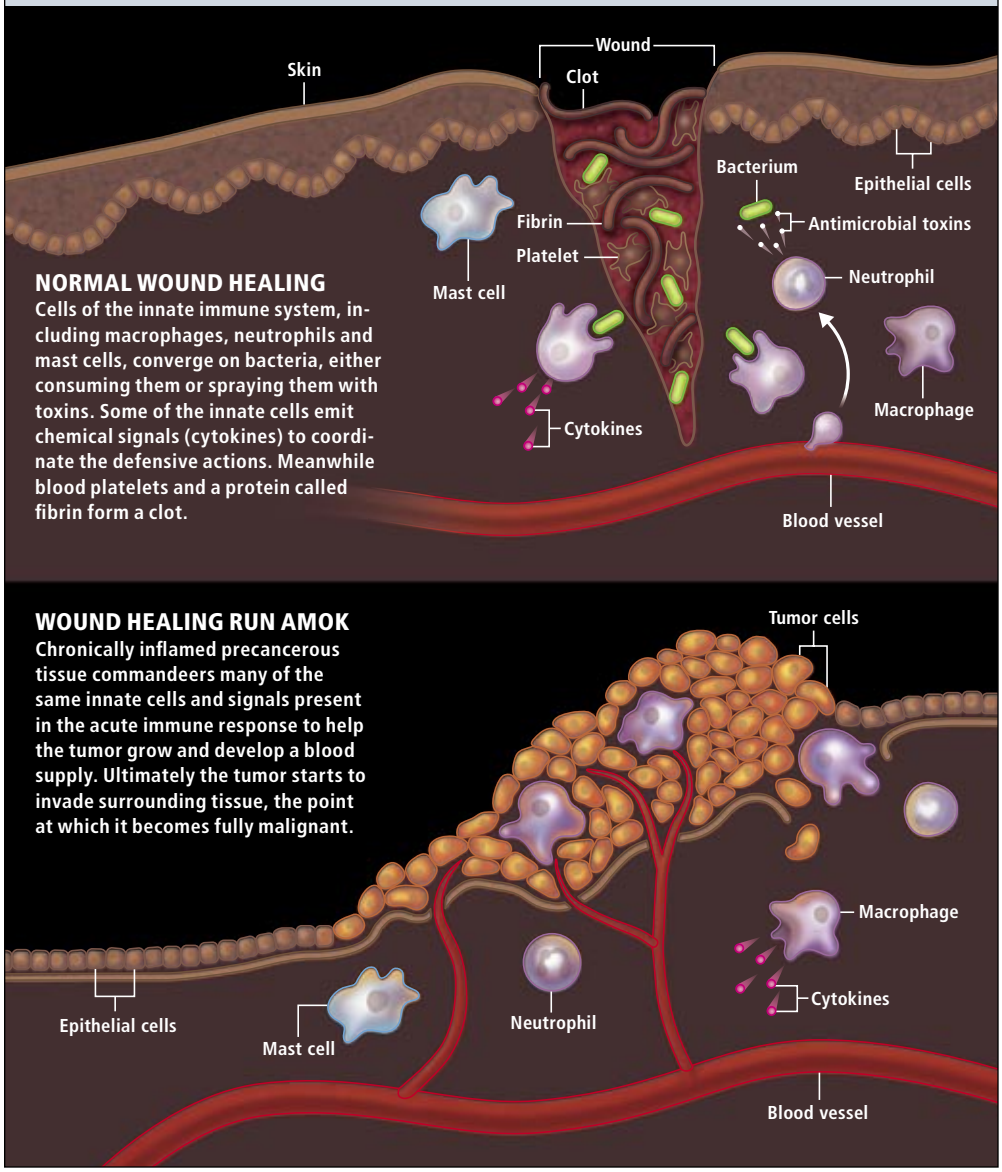
The ready availability of knockout mice, in which the effects of selectively switching off genes could be tested, helped to highlight the cancer-inflammation link. Coussens and her U.C.S.F. colleagues Douglas Hanahan and Zena Werb reported in 1999 that mice engineered with activated cancer genes but without mast

cells (another type of innate immune cell) developed premalignant tissue that did not progress to full malignancy. In 2001 Jeffrey W. Pollard and his co-workers at the Albert Einstein College of Medicine described mice that were genetically engineered to be susceptible to breast cancer tumors but that produced precancerous tissue that did not turn fully malignant unless it enlisted the assistance of macrophages.

The altered picture does not completely overturn the old one. In fact, it reveals that the immune system functions as a double-edged sword. The network of molecules and cells, second in complexity only to the brain, remains a paradox: sometimes it promotes cancer; other times it hinders disease. Some types of innate immune cells, such as natural killer cells, can actually protect against tumor growth. Others may nurture a malignancy only when the microenvironment is "polarized" into an inflammatory state; when not, they may blot it out. Inflammation, moreover, produces tumors in many organs, but not all—and its link to blood-borne cancers is not well characterized.

CANCER HIJACKS WOUND HEALING

Innate immunity responds to an insult, such as a puncture wound, with a cellular and chemical arsenal. Cancer biologists have recently begun to understand how chronically inflamed premalignant tissue uses many of the same biochemical players to promote cancer development.



NORMAL WOUND HEALING
Cells of the innate immune system, including macrophages, neutrophils and mast cells, converge on bacteria, either consuming them or spraying them with toxins. Some of the innate cells emit chemical signals (cytokines) to coordinate the defensive actions. Meanwhile blood platelets and a protein called fibrin form a clot.

WOUND HEALING RUN AMOK
Chronically inflamed precancerous tissue commandeers many of the same innate cells and signals present in the acute immune response to help the tumor grow and develop a blood supply. Ultimately the tumor starts to invade surrounding tissue, the point at which it becomes fully malignant.

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CANCER BASICS

A developing malignancy proceeds in stages—a process that may take years, even decades, to fully evolve.

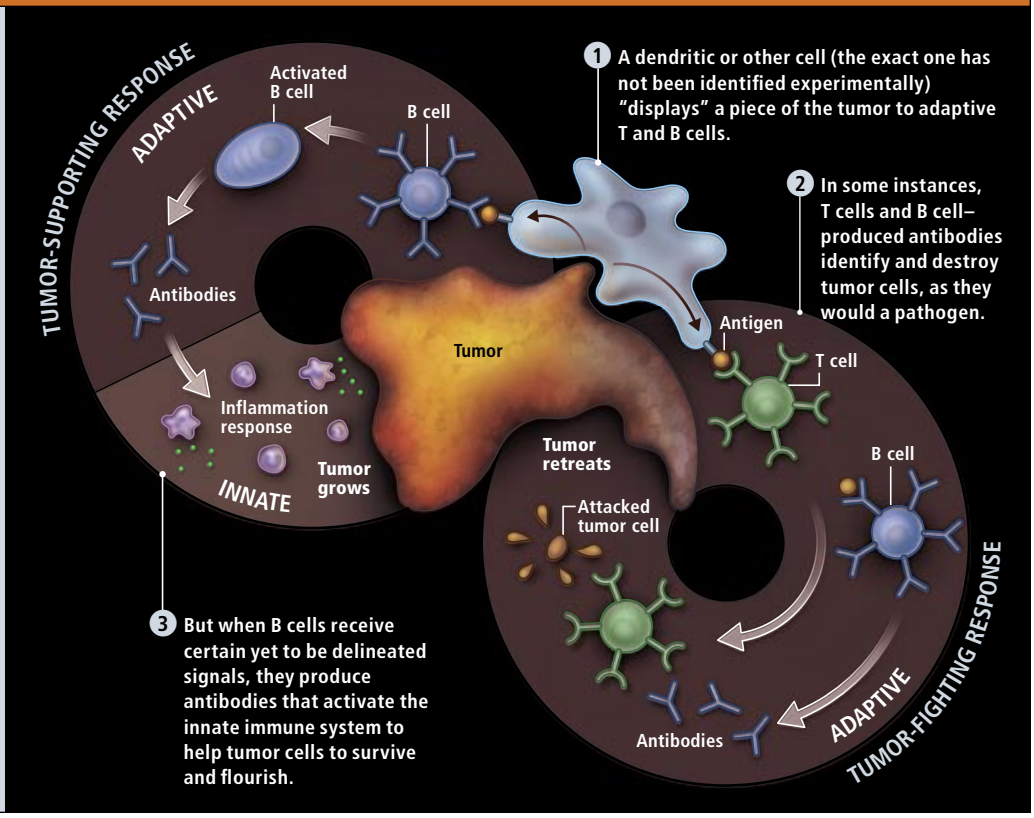
INITIATION
Hereditary mutations or exposure to chemicals or radioactivity results in genetic changes in one or more cells.

PROMOTION
Cells in premalignant tissue begin to proliferate, often in the presence of an inflammatory stimulus. Their appearance becomes increasingly abnormal.

PROGRESSION
Tumor cells begin to invade surrounding tissue and to spread to the blood and lymph nodes, at which point full malignancy develops. Metastases may establish themselves at distant sites.

THE IMMUNE PARADOX

Two arms of the immune system—the innate and the adaptive—are exquisitely well adapted for fighting pathogens, but their role in combating cancer is decidedly more paradoxical. The innate system furnishes an initial inflammatory response to a microbial insult by attacking any invading pathogen indiscriminately, whereas adaptive immunity furnishes a delayed response that homes in on a particular pathogen. In cancer, both systems may sometimes attack tumor cells. But a tumor protects itself by recruiting the innate system to enhance its development.



Genetic damage is the match that lights the fire of malignancy, and inflammation is the fuel that feeds the flames.

When looking for culprits, researchers have often focused their microscopes on macrophages, which occupy a meaningful spot among the white blood cells in the tumor microenvironment. The macrophages are capable of killing tumor cells or sending out an alarm to T cells of the adaptive immune system that something is amiss. But work by Pollard and other researchers has detailed how macrophages are "reeducated" by cancer cells to do their bidding. They become factories for cytokines and growth factors that nurture tumor development.

Turning the macrophages into traitors begins when tumor cells send out help signals that attract cells that become macrophages once they reach the tumors. Inside the tumors, proliferating cells grow so quickly that they begin to die for lack of oxygen. A combination of hypoxia and messages from the tumor cells initiates a process whereby the newly arrived macrophages assume their bad-body identity as tumor promoters. Cancer biologists give the name tumor-associated macrophages to these mutineers that congregate in and around the tumor.

Biologists have now been able to follow the inflammation link down to the level of individual signaling molecules, providing harder evidence for a connection to carcinogenesis. For example, nuclear factor-kappa B (NF-κB) is a complex of proteins that acts as a master switch for turning inflammation genes on and for controlling cell death. As biological pathways go, NF-κB's is world-famous, having been discovered and patented for use in drug development by scientific stars that include Nobelists David Baltimore and Phillip A. Sharp and having subsequently become the object of multimillion-dollar patent litigation.

In 2004 Yinon Ben-Neriah and Eli Pikarsky of the Hebrew University of Jerusalem and their colleagues reported that mice engineered to develop hepatitis (which can cause liver cancer) contracted precancerous lesions that did not progress to full malignancy when NF-κB was curtailed through a genetic alteration or when the proinflammatory TNF signaling molecule was shut off. In the latter group, a neutralizing antibody blocked TNF and prevented it from binding to a receptor on the premalignant liver cells; loss of the receptor prevented the TNF from triggering a molecular cascade that turns on the NF-κB master switch. Blocking NF-κB prompted the precancerous liver cells to initiate apoptosis, or programmed cell death. In a relat-

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ed finding that year, Michael Karin and his collaborators at the University of California, San Diego, found that inhibiting NF-κB in mice engineered to develop colitis, which can lead to colon cancer, also promoted apoptosis. And shutting down the pathway in inflammatory cells, such as macrophages, deterred tumor development as well.

So far the clearest evidence of a link between cancer and inflammation is the data demonstrating that inflammation encourages the conversion of precancerous tissue to full malignancy for many cancers. But the biological response may also be involved in initiating the disease and in advancing metastasis. Infections with *Helicobacter pylori* bacteria induce inflammation that greatly increases the risk of gastric cancer, and the hepatitis C virus can bring on liver cancer, to name just two cancers. Pathogens may also generate free radicals, which can damage DNA. But although inflammation may be involved from the outset, few studies have shown yet that an inflammatory condition actually alters DNA to provide the initiating spark.

The case for a role in metastasis is stronger—and recent studies lend credence to this hypothesis. Karin's group reported in the April 5 *Nature* that inflammation, not genetic changes in cancer cells, spurs metastasis in mice engineered to acquire prostate cancer. The research suggests that a cytokine produced by inflammatory cells near a prostate tumor induces tumor cells to decrease production of a protein that blocks metastasis. This result, Karin notes, may explain the puzzling observation that cutting into tumors, such as for a prostate biopsy, sometimes seems to encourage metastasis. If he is correct, the inflammation generated by the intervention could be at fault. Around the same time, Pollard's group reported in *Cancer Research* on a study in mice that observed that macrophages accompany breast tumor cells in their migration

Immune System as Cancer Fighter

Tumors waylay the immune system to promote their own growth and survival. But the opposite also holds. The antibodies and killer T cells of the adaptive immune system can, at times, target and destroy cancer cells. Drug companies and scientists have tried to turn this knowledge into new therapies, with mixed results.

Among the most successful new biotechnology drugs are monoclonal antibodies—identical antibodies that are capable of attacking a cancer antigen, a molecular fragment found on the surface of a cancer cell. Monoclonals are generally a "passive" immunotherapy because they are produced in cell culture or in mice and injected into patients instead of relying on the patient's own immune system to produce antibodies.

In contrast, cancer vaccines—the object of a frustrating decades-long quest—are "active" therapies. A patient receives an injection of an antigen, usually along with another helper molecule, an adjuvant, that precipitates an immune response.

Cancer antigens are more difficult to identify than those for pathogens because cancer cells are mutant forms of the body's own cells. The adaptive immune system often does not see them as foreign—and a tumor can trick the body into turning off any immune response that does arise.

After hundreds of previous trials, and the absence of virtually any evidence from them that vaccines cause tumors to regress, the concept of the cancer vaccine has garnered its share of critics. "When you give cancer vaccines, sometimes you raise T cells against the vaccines, but they're just not powerful enough to keep the cancer from growing," notes Steven A. Rosenberg, chief of surgery at the National Cancer Institute. Rosenberg and his co-workers have pursued a different approach, adoptive cell transfer, in which T cells that target tumors are selected from white blood cells removed from the body. They are then multiplied in the laboratory and reinfused into patients whose immune systems have been chemically suppressed. In a 2005 study in the *Journal of Clinical Oncology,* about half of 35 melanoma patients saw their metastatic tumors regress at least partially.

In recent months, the picture for cancer vaccines has brightened somewhat. Early positive reports were presented at the American Association for Cancer Research in April for vaccines for breast, prostate, and head and neck cancers. But in May came more bad news: the Food and Drug Administration delayed approval of what would have been the first U.S. therapeutic cancer vaccine formulated by Seattle-based Dendreon for prostate cancer [see "Overcoming Self," by Gary Stix; SCIENTIFIC AMERICAN, July 2004].

Marshaling the patient's own immune system to fight cancer may still be possible. But meeting that goal may well depend on deepening the growing understanding of how the immune system serves as a two-edged sword that can either foster or block cancer progression. —*G.S.*

COMMON CAUSE

Chronic inflammation contributes to many diseases, not just cancer.

HEART DISEASE

Macrophages, stars of innate immunity, are key players. They ingest "bad" cholesterol (low-density lipoproteins), and then the cells are encased in a fibrous cap that forms arterial plaque, which can break off and create a clot that blocks an artery, leading to a heart attack.

DIABETES

When exposed to the metabolic stress that occurs from being obese, both innate immune cells and fat cells (adipocytes) manufacture signaling molecules called cytokines such as tumor necrosis factor. These molecules interfere with the normal function of insulin and can lead to diabetes.

ALZHEIMER'S DISEASE

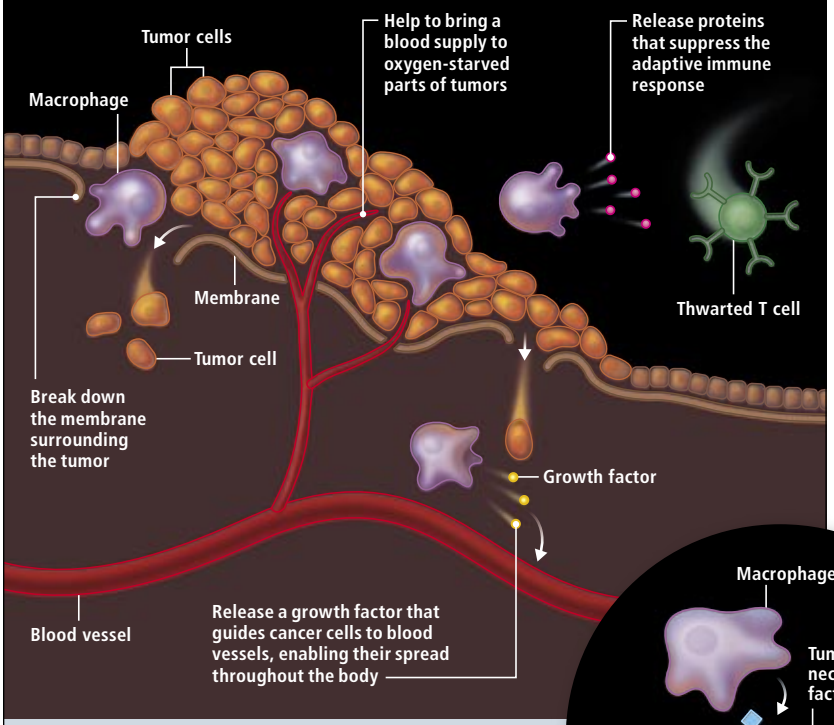
Microglial cells, the neural equivalent of macrophages, express cytokines and cell-damaging free radicals, while interacting with the beta-amyloid proteins that build up in the plaques that are characteristic of the disease. The resulting inflammation can damage neurons.

DEPRESSION AND SCHIZOPHRENIA

High levels of inflammatory molecules—interleukin-6 and C-reactive protein—have been found in depressed patients. Some evidence even suggests that elevated cytokines correlate with schizophrenia.

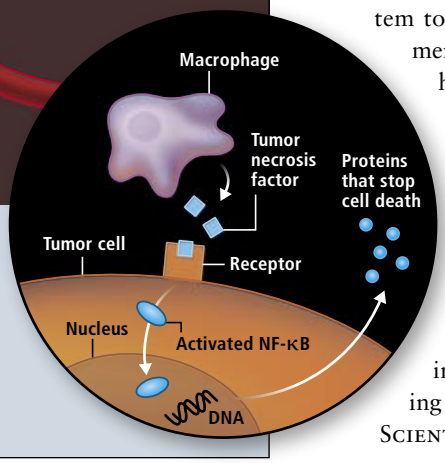
THE BIG EATERS

Macrophages, also known as big eaters, are inflammatory cells that coordinate many critical steps in cancer development, from nurturing the tumor to helping its cells spread to distant sites.



A MASTER SWITCH ▶

Macrophages produce inflammatory compounds, such as tumor necrosis factor, which can activate a gene switch, a complex of proteins called nuclear factor-kappa B (NF-κB), in a tumor cell. NF-κB enters the cell nucleus and turns on production of proteins that stop cell death and promote inflammation and cell proliferation.



toward blood vessels that will transport them to remote sites, all the while sending chemical messages to their partners.

The innate immune system has received the most attention in explorations of how inflammation might cause cancer. As with innate immunity, the adaptive immune system—the T cells and antibodies produced by B cells that target specific molecules on invading cells—contributes to pathology or may also fight against it. For decades, immunotherapies designed to enhance T cell responses against cancer have been explored, though often with disappointing results [*see box on preceding page*].

Furthermore, an emerging picture has begun to reveal an intricate cross talk between innate and adaptive immune cells that may participate in the promoting of malignant disease. Researchers working on cancer vaccines may need to take account of these interactions in designing their treatments if they are ever to prove effective. One study showed that ovarian tumors produce a signaling molecule that serves to attract regulatory T cells, a subclass of adaptive immune cells responsible for quieting other T cells [see "Subduing Suppressors," by Lisa Melton; Scientific American, December 2002].

Meanwhile Coussens and her colleagues at U.C.S.F. found in a 2005 study published in *Cancer Cell* that the removal of antibody-making B cells from mice engineered to be prone to skin cancer prevented the tissue changes and angiogenesis that are prerequisites for disease progression. In their normal role as pathogen fighters, B cell–produced antibodies circulate through the bloodstream and mark viruses and bacteria for destruction by innate immune cells. In response to a signal from precancerous tissue, however, the antibodies induce the innate system to collaborate in cancer development. An open research question is how this process starts. One possibility suggests that a cancer cell may send a message to innate immune cells, perhaps dendritic cells, that then activate B cells. Signaling may involve toll-like receptors, which have emerged as prominent intermediaries in innate immune messaging [see "Immunity's Early Warning System," by Luke A. J. O'Neill; Scientific American, January 2005].

Cancer Blockers

The recognition that cancer is more like an organ than just a clump of cells with DNA mutations in cell nuclei may also explain why some of the previous approaches to chemotherapy have met with limited success. "People have taken cells and then transformed them in culture and stuck them into animals," Pollard says. "They grow as little balls. They do certain things there. But they are not complex tissues, whereas a naturally occurring tumor is a very complex tissue."

Instead of just killing cancer cells—the goal of current drug therapies and radiation—new approaches may supplement existing drugs by slowing inflammation. Without the involvement of macrophages and other innate cells, the premalignant tissue would remain in check.

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Cancer could, in essence, become a chronic disease akin to rheumatoid arthritis, another inflammatory condition. "Keep in mind almost no one dies of primary cancer," says Raymond DuBois, provost of the University of Texas M. D. Anderson Cancer Center and a researcher of anti-inflammatory agents for cancer. "A patient almost always dies from a metastasis."

A pharmaceutical against chronic inflammation represents a more alluring proposition than massacring malignant cells (and, unavoidably, healthy ones), a consequence of existing chemotherapies. Taken alone, such an agent might be benign enough to use every day as a preventive for high-risk patients. Epidemiological and clinical studies have shown some promise for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin to stave off the onset of some solid tumors. Investigations continue on more selective blocking of the production of prostaglandins, the regulatory molecules that are curtailed by NSAIDs. In particular, drugs that inhibit production of prostaglandin E_2 may curb inflammation and tumor growth, while avoiding the cardiovascular side effects of drugs such as Vioxx and the gastrointestinal problems of the earlier class of NSAIDs [see "Better Ways to Target Pain," by Gary Stix; Scientific American, January 2007]. The anti-inflammatory effects of the ubiquitous statins used to lower cholesterol are also being contemplated.

Some treatment options already exist. The drug Avastin inhibits production of the angiogenesis-promoting VEGF, although oncologists must contend with other molecules in the tumor microenvironment that promote blood vessel growth. Drugs developed for more familiar inflammatory diseases may also fight cancer—and these medicines might be combined into HIV-like drug cocktails, that also include angiogenesis inhibitors and cell-killing agents.

Inhibitors of TNF have received approval for treatment of rheumatoid arthritis, Crohn's disease and other disorders and are now in clinical trials for both solid tumors and blood cancers. The drug Rituxan, a monoclonal antibody that represses B cells in rheumatoid arthritis and B cell lymphoma, might prevent the inflammatory response that fuels formation of solid tumors. Other cytokines and related molecules (IL-6, IL-8 and CCL2, among others) are also potential targets, as is NF-κB.

Some existing compounds, including NSAIDs and even one found in the spice turmeric, exert at least some of their effects by inhibiting NF-κB. But major pharmaceutical laboratories are investigating highly selective inhibitors of this molecular linchpin, many of them targeted at the enzymes (such as I-κB kinase) that regulate NF-κB activity.

A Chemical Trojan

One group is contemplating a radically ambitious treatment, a molecular Trojan horse of sorts. Claire Lewis and Munitta Muthana of the University of Sheffield in England and their colleagues have designed a drug delivery scheme that takes advantage of the natural attraction of macrophages to the oxygen-starved areas in tumors. They have engineered macrophages to deliver a therapeutic virus to hypoxic tumor regions, which respond poorly to conventional treatments such as chemotherapy and radiation because of an insufficient blood supply. Once the macrophages arrive in a tumor (grown in culture so far), each one releases thousands of copies of the virus, which then infect the cancer cells, after which a protein in those cells activates the therapeutic gene in each virus. This action then directs synthesis of a cell-killing toxin. "The macrophage is migrating into a site and doing what we want it to do rather than driving tumor development in a normal way," Lewis says.

The exact outlines of an anti-inflammatory strategy against cancer have yet to be elucidated. Tweaking immune cells that form a defensive barrier against pathogens bears its own risks. "It's a very complicated issue," DuBois notes. "If you magically shut down the immune system, you will have problems with opportunistic infections, just like with AIDS." Use of TNF blockers in other inflammatory disorders has been linked to tuberculosis and other infections, even potentially lymphoma. Moreover, inhibiting the NF-κB pathway can paradoxically promote cancer in some instances. Constraining NF-κB can at times lead to tissue damage and a process of abnormal regeneration of that tissue that can foster cancer.

Still, it seems likely that a new generation of anti-inflammatory agents will join the chemotherapeutic arsenal. Chronic diseases—and their underlying inflammatory conditions—are hallmarks of an aging population. "We're all a little bit overinflamed," Pollard observes. Treating the smoldering embers that surround the tumor rather than just mutant cells could make cancer a disease we can live with. ■

Instead of killing cancer cells—the goal of current drug therapies and radiation—new chemotherapies may supplement existing drugs by turning down inflammation.

MORE TO EXPLORE

Smoldering and Polarized Inflammation in the Initiation and Promotion of Malignant Disease. Frances Balkwill, Kellie A. Charles and Alberto Mantovani in *Cancer Cell,* Vol. 7, No. 3, pages 211–217; March 2005.

Distinct Role of Macrophages in Different Tumor Microenvironments. Claire E. Lewis and Jeffrey W. Pollard in *Cancer Research,* Vol. 66, No. 2, pages 605–612; January 15, 2006.

Paradoxical Roles of the Immune System during Cancer Development. Karin de Visser, Alexandra Eichten and Lisa M. Coussens in *Nature Reviews Cancer,* Vol. 6, No. 1, pages 24–37; January 2006.