

Understanding Cancer Diversity

<http://www.hhmi.org/biointeractive/understanding-cancer-diversity>

The human body operates, in essence, like a large, multicellular society. Within this tight-knit community, trillions of cells, organized into hundreds of different tissues, collaborate for the good of the whole organism. Some cells convert food into energy, some transport oxygen or nutrients throughout the body, some fight infections, and some shuttle the organism's genes into the next generation.

Cancer occurs when a single cell acquires the ability to reproduce aggressively and to invade other tissues. This rebellious cell shuns its normal role, instead multiplying and ultimately colonizing areas of the body where it doesn't belong. Left unchecked, this anarchy destroys the cellular society. It interferes with the body's normal function, destroys organs, and eventually kills the organism.

Once cancers have spread, they are difficult to eradicate because cancer cells come from the body itself. The body's immune system is unable to distinguish cancer cells from normal ones. Antibiotics are useless—they are designed to eliminate microbial invaders. Chemotherapy and radiation can kill cancer cells, but they also kill other cells in the body.

The search for a cure is complicated by the fact that cancer is not one disease. Physicians and researchers recognize at least 200 types of cancer—that's approximately as many cancers as there are types of tissue in the body. Although they share similar basic characteristics—the ability to reproduce vigorously and to invade foreign tissues—each cancer is different in terms of its prognosis and treatment. Its properties depend on the type of tissue from which it arose and on which tissues it subsequently invades.

Although this diversity presents a challenge, it also offers hope. By learning about the molecular aberrations that drive cancers, researchers such as HHMI's Bert Vogelstein have enhanced our understanding of the basic biology of this group of diseases. What's more, they have developed techniques that will allow them to characterize individual tumors—tools that in future should allow doctors to screen people for their predisposition to cancer, to detect tumors that are not yet visible, and to select the treatment most effective for eliminating a particular cancer.

What is Cancer?

Cancer cells share two basic properties. First, they proliferate in defiance of the normal constraints that keep cell growth and division in check. And second, they invade and colonize territories normally inhabited by other cells.

Cells that have the first property will divide over and over to form a small, self-contained mass called a tumor. Such tumors are considered benign because they are restricted to one site in the body and can usually be surgically removed—cleanly and completely—with few complications.

But increased cell proliferation alone is not enough to cause cancer. A tumor is considered cancerous only if its cells have the ability to invade surrounding tissue, in which case it is said to be malignant. Malignant cells can break loose from the primary tumor, enter the bloodstream or lymphatic vessels, and form secondary tumors at other sites in the body. The more widely the cancer spreads, the harder it becomes to eradicate. This metastasis is what makes cancer so deadly.

Different Cells, Different Cancers

Any cell type can give rise to a cancer—some even give rise to several different types. Cancers are generally classified by their tissue of origin. Sarcomas, for example, come from connective tissue or muscle. Carcinomas arise from the epithelial cells that line the body's organs. Hippocrates coined the name for this common type of malignant cancer from the Greek word for crab (*karkinos*), because physicians thought that these tumors resembled the claws of a crab.

Some 90 percent of human cancers are carcinomas. Why some cells are more likely to become cancerous than others is complex and not entirely understood. The tendency for any cell to develop into cancer undoubtedly involves its natural propensity for proliferation. Cells that divide more rapidly are closer to behaving like cancers than those that divide slowly or not at all. In addition, cells that are exposed to cancer-causing mutagens—agents that change the nucleotide sequence of DNA—are more likely to become malignant. Finally, cells that have trouble detecting and repairing damaged DNA are more likely to become cancerous. Such cells have a greater tendency to accumulate the mutations that promote the growth and spread of cancer.

Different Genes, Different Cancers

Scientists have identified hundreds of genes that are mutated in cancers, and each cancer is characterized by its own array of genetic lesions. Different combinations of genes are altered in different forms of cancer—and even in patients that appear to have the same form of the disease. Certain genes always go hand in hand with particular cancers. Mutations in a gene called *APC*, for example, occur largely in colon cancers. Other genes, such as *p53*, are involved in a variety of human cancers.

Researchers are actively investigating why certain genes are associated with particular cancers. It might have something to do with how different cells use these genes. Each cell in the body, whether it is a heart cell or a liver cell or a blood cell or a brain cell, receives the same set of genes. But perhaps cells that line the colon rely heavily on *APC* to control their growth and proliferation, whereas other cells in the body have chosen different genes to perform that critical task. In the case of *p53*, perhaps all cells use this gene to monitor their DNA for damage and then decide whether to divide or self-destruct.

Finally, exposure to different cancer-causing agents can influence which type of cancer will form. For example, chemicals present in cigarette smoke cause specific kinds of mutations in the *p53* gene. These lesions are frequently seen in lung cancer but not other kinds of cancer. Aflatoxin, a toxic molecule produced by a mold that grows on improperly stored peanuts and grains, generates a different mutation in the *p53* gene—one associated with liver cancer. UV radiation causes yet a different type of *p53* mutation that is found in 90 percent of patients with skin tumors but rarely in cancers of the liver or lung. Tracing mutations to a particular carcinogen can alert health officials to the presence of cancer-causing chemicals in the environment, and appropriate measures can then be taken to eliminate people's exposure to these chemicals.

Is Cancer Hereditary?

For the most part, the answer is no. Cancer is a genetic disease in that it is caused by mutations that alter the function of our genes. Most of these mutations, however, are not inherited but occur after birth. Because these changes usually occur in body cells other than the sperm and eggs that carry the person's DNA into the next generation, they are not passed on. A portion of these genetic lesions result from interactions with cancer-causing elements in the environment, such as sunlight and tobacco smoke. Smoking is a major source of carcinogens. If we could eliminate the use of tobacco, we could prevent about 30 percent of all cancer deaths.

The majority of cancer-causing mutations, however, arise within cells without any help from outside agents. Cells can make mistakes while copying their DNA and then fail to repair them, for example. These genetic errors are a major source of the types of mutations associated with cancer.

That said, certain types of cancers can run in families. In this case, individuals inherit a mutation that predisposes them to developing cancer. Certain families, for example, carry a mutation that knocks out the activity of a single copy of the *APC* gene. Children in these families inherit an increased risk for developing colon cancer.

Exploiting Diversity

Thanks to our studies of cancer genetics, we now know that cancer is not a single disease but a collection of diverse yet related diseases. Our ability to determine which genes are altered in a particular tumor should help doctors tailor

treatments to individual patients. Furthermore, the discovery that some of the same types of genetic lesions crop up again and again in different tumors suggests that there may be only a limited number of ways in which cancers can breach our cellular defenses—and offers hope that we can develop therapies that will tackle these diseases.

The Evolution of Cancer

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A cancer cell accumulates mutations, each of which can give the cell a growth advantage over its neighbors. This single cell will divide to populate the tumor until another cell with an even better growth advantage crops up. At that point, the more aggressive cell reproduces rapidly, taking over the tumor. It's survival of the fittest, with every cell for itself.

But all these cancer-promoting mutations do not occur at once. At each stage, cancer cells face selective pressures that drive their evolution. Cells near the center of a growing tumor, for example, face shortages of oxygen and nutrients. And pioneering cells that escape the main tumor must adapt to life in a foreign tissue if they are to establish outposts in other organs of the body. Only those cells that acquire mutations that help them adapt to the changing environment and outcompete their neighbors will survive to divide and conquer.

For a cell to become cancerous, it must amass quite a few mutations—sometimes three or four but often many more. And these mutations must occur in the correct genes and in the correct place within those genes. That combination is, fortunately, statistically rare. What's more, the process of acquiring multiple mutations can take decades. Most of us die from other diseases before cancer has had time to develop.

Although cancer-causing mutations can occur in several kinds of genes, all these mutations ultimately promote cell growth and survival, allowing cell division to outstrip cell demise. Bert Vogelstein and his colleagues have spent years identifying the specific genes and mutations responsible for colon cancer. This type of cancer is a good one to study because the resulting tumors can be removed and analyzed at various stages in their development, revealing the genetic progression that leads to cancer. Vogelstein's studies of colon cancer have opened a window on cancer evolution and led to a deeper understanding of the formation and development of all cancers.

Loss of Control

The growth of a cancer is often likened to a car speeding out of control. Whether the car's brakes are cut or its gas pedal is stuck, the vehicle hurtles forward, no longer responding to the driver's attempts to control its speed. In a sense, the same thing happens in tumors, which form when normal cells lose the ability to control their growth and division. That loss of control can result from a number of different mutations. Cancer cells can activate genes that encourage proliferation—akin to giving the car too much gas. Such growth-promoting genes are called oncogenes, from *onkos*, the Greek word for tumor or mass. Cancer cells can also eliminate genes that inhibit replication—cutting the brakes that normally keep cell growth in check. These growth-inhibiting genes are called tumor suppressors. Mutations that activate oncogenes or inhibit tumor suppressors all promote cancer by upsetting the normal balance between cell birth and cell death.

Mr. Bad Wrench

Cancers can also speed their growth by acquiring mutations in genes that normally fix DNA damage. By disabling their cellular repair systems—the equivalent of hiring an inept mechanic—cancer cells further tip the balance in their favor. Shutting down DNA repair allows any mutations that crop up to be preserved. Thus mutations in repair genes promote the accumulation of additional mutations, fueling the evolution of cancer.

Defects in DNA repair genes are responsible for one of the most common forms of hereditary colon cancer, called hereditary nonpolyposis colorectal cancer (HNPCC). Patients with HNPCC inherit a defective copy of an important repair enzyme that fixes the errors that sometimes occur as cells copy their DNA. Once cells lose their ability to repair these replication errors, mutations can accumulate in many genes, including tumor suppressors and oncogenes. Patients with this genetic defect develop one or two tumors that then progress rapidly to full-blown cancer.

A Model Cancer

Colorectal tumors begin as benign polyps—small outgrowths in the lining of the colon. Then, as mutations occur in genes that normally balance the relative rates of cell birth and cell death, the tumors grow larger. Eventually, the cells break away from the tumor and colonize the liver, lungs, and other tissues in the body. At this point the tumor is considered a malignant cancer.

In many colon cancers, a mutation that inactivates a tumor-suppressor gene called *APC* is the first, or at least a very early, step in cancer progression. *APC* mutations can be detected in small benign polyps at the same high frequency as in large malignant tumors, suggesting that they occur early in the process. The loss of *APC* activity gives the affected cell a growth advantage, allowing it to form a colony of cells that divide more rapidly than they die. The increased proliferation leads to the growth of a polyp.

Mutations that activate an oncogene called *Ras* take place later than those that knock out *APC*. *Ras* mutations are rare in small polyps but common in larger ones. Activation of oncogenes such as *Ras* enables the tumor to grow larger still. Elimination of other tumor-suppressor genes, such as *p53*, comes much later. Finally, additional changes—still poorly understood—permit the tumor to become invasive and spread to other tissues. Mutations that eliminate the activity of DNA repair genes, which can occur at any time, further help drive the process forward.

Putting Knowledge to Work

Knowing the genetic path that a particular cancer follows could someday help physicians better treat individual patients. By determining the genetic defects responsible for a specific cancer, physicians might be able to select the therapy that will be most effective at eliminating that cancer. Furthermore, each cancer-causing gene that researchers identify can serve as a target for the development of more specific therapies that will wipe out cancer cells while leaving healthy cells unharmed.