Researchers have uncovered processes that make cancer even more complicated than they thought it was.

By George Johnson

MEDICINE

THE LONG TRAIL OF CANCER'S CLUES

Things are rarely as simple as they seem, and what appears to be complex may be no more than ripples on the surface of a fathomless ocean. The mechanics of malignancy—a single cell acquiring mutation upon mutation until it spirals down the rabbit hole of cancer—was neatly described by two scientists, Douglas Hanahan and Robert A. Weinberg, in a sweeping synthesis published in 2000 called “The Hallmarks of Cancer.”

The idea of cancer occurring as an accumulation of mutations to a normal cell goes back decades. But it was Hanahan and Weinberg who assimilated a growing mass of laboratory results and theoretical insights into six characteristics that a cancer cell must acquire as it develops into the would-be creature called a tumor. It must acquire the ability to stimulate its own growth and to ignore signals admonishing it to slow down (that is where oncogenes and tumor suppressors come in). It must learn to circumvent the fail-safe mechanisms that cause even slightly disabled cells to destroy themselves and to defeat the internal counters—the telomeres found on the ends of chromosomes—that normally limit the number of times a cell is allowed to divide. It must learn to initiate angiogenesis—the sprouting of its own blood vessels—and finally to eat into surrounding tissue and to metastasize.

More than a decade after it was published, “Hallmarks” was still the most frequently cited paper in the history of the prestigious journal Cell, which is as good as saying that it may be the single most influential paper on the biology of cancer. Known as the monoclonal theory (a dividing cell and its branching tree of descendents is called a clone), the picture spelled out in “Hallmarks” remains the dominant paradigm, like the big bang theory is in cosmology. Creation began as a sin-
gularity—a primordial dot of mass-energy—and ballooned to form the universe. A cancer begins with one renegade cell—it was Weinberg who popularized that term—expanding to form a tumor. With this rough map in place, the two scientists looked forward to a renaissance in the understanding of cancer:

With holistic clarity of mechanism, cancer prognosis and treatment will become a rational science, unrecognizable by current practitioners.... We envision anticancer drugs targeted to each of the hallmark capabilities of cancer.... One day, we imagine that cancer biology and treatment—at present, a patchwork quilt of cell biology, genetics, histopathology, biochemistry, immunology, and pharmacology—will become a science with a conceptual structure and logical coherence that rivals that of chemistry or physics.

A physics of cancer! That still may happen. But in the decade and more that has passed since the paper's immodest prediction, scientists have continued to uncover whole new layers of complications.

BEYOND MUTATIONS
INSIDE THE BIOLOGICAL MICROCHIP called a cell there are components inside components and wiring so dense and so fluid that it sometimes seems impossible to tease the strands apart. Moving up a level, what is happening inside a cancer cell cannot be fully understood without considering its place within an intricate communications network of other cells. By the time the "Hallmarks" paper was published, scientists were already finding that tumors are not homogeneous masses of malignant cells—that they also contain healthy cells that help produce the proteins a tumor needs to expand and attack tissue and to plug into the blood supply. This aberrant ecosystem has come to be called the cancer microenvironment, and entire conferences and journals are devoted to understanding it.

Complicating matters further has been the gradual realization that the genetic changes that can lead to cancer do not necessarily have to occur through mutations—deletions, additions or rearrangements of the nucleotide letters in a cell's DNA. The message can be altered in more subtle ways.

Molecular tags can bind to a gene in a way that causes it to be disabled—in capable of expressing its genetic message. (The tags are methyl groups, so this process is called methylation.) Genes can also be enhanced or suppressed by twisting the shape of the genome. In the iconic image, DNA's interwoven coils float as elegantly as jellyfish in lonely isolation. But in the messiness of the cell, the two helical strands are wrapped around clusters of proteins called histones. Methyl groups and other molecules can bind to the helix itself or to its protein core and cause the whole assembly to flex. As that happens, some genes are exposed and others are obscured.

Such alterations, which change a cell's function while leaving its DNA otherwise unscathed, are called epigenetic. Epi, from ancient Greek, can mean "over," "above" or "on." Just as a cell has a genome, it also has an epigenome—a layer of software overlaying the hardware of the DNA. Like the genome itself, the epigenome is preserved and passed on to daughter cells.

What all this research suggests is that cancer may not be only a matter of broken genes. Disturbances in a cell—carcinogens, diet or even stress—might rearrange the epigenetic tags without directly mutating any DNA. Suppose that a methyl group normally keeps an oncogene—one that stimulates cellular division—from being expressed. Remove the tag, and the cell might start dividing like crazy. On the other hand, the production of too many tags might inactivate a tumor suppressor gene that would normally hold mitosis in check. Freed to proliferate, the cell would be vulnerable to more copying errors. So epigenetic changes could lead to genetic changes—and these genetic changes could conceivably affect methylation, triggering more epigenetic changes ... and round and round it goes.

Outside the laboratory, enthusiasm for this scenario is driven both by hope and by fear. Epigenetics might provide a way for a substance to act as a carcinogen even though it has been shown incapable of breaking DNA. But unlike genetic damage, these changes might be reversible. How big a role epigenetics plays remains uncertain. Like everything that happens in a cell, methylation and the modification of histones are controlled by genes—and these have been found to be mutated in different cancers as well. Maybe it all comes down to mutations after all.

On the other hand, a few scientists have proposed that cancer actually begins with epigenetic disruptions, setting the stage for more wrenching transformations.

Even more unsettling is a contentious idea called the cancer stem cell theory [see "Stem Cells: The Real Culprits in Cancer?" by Michael F. Clarke and Michael W. Becker; SCIENTIFIC AMERICAN, July 2006]. In a developing embryo, stem cells are those with the ability to renew themselves indefinitely—dividing and dividing while remaining in an undifferentiated state. When a certain type of tissue is needed, genes are activated in a specific pattern, and the stem cells give rise to specialized cells with fixed identities. In brief: What prompts certain cells to become cancerous and grow into tumors? For a while researchers figured the answer lay entirely in the way key genes became damaged, or mutated, over time. Over the past decade, however, investigators have uncovered many other contributing factors—from bacteria living in the intestine to epigenetic switches that turn various genes on and off. Unraveling this growing complexity makes understanding cancer harder than ever, but it also offers unexpected avenues to explore for the development of new treatments.
Once the embryo has grown into a creature, adult stem cells play a similar role, standing ready to differentiate and replace cells that have been damaged or have reached the end of their life. Because healthy tissues arise from a small set of these powerful forebears, why couldn’t the same be true for tumors?

This would be an unexpected twist on the conventional view in which any cancer cell that has acquired the right combination of mutations is capable of generating a new tumor. Imagine if instead the growth and spread of a cancer is driven by a fraction of special cells, those that somehow become endowed with an intrinsic quality called “stemness.” Only the cancer stem cells would have the ability to replicate endlessly, metastasize and seed another malignancy. How much easier that might make things for oncologists. Maybe chemotherapies fail because they spare the cancer stem cells. Remove these linchpins, and the malignancy would collapse.

As I struggled to fit this all into the big picture, I was relieved to find researchers who seemed as baffled as I was. However it all pans out, the underlying view of cancer as a Darwinian process—arising like life itself through random variation and selection—would remain unshaken. But as an outsider trying to understand the essence of cancer, I felt daunted by the possibility of even more convolutions.

In the end, all biology comes down to genes talking to genes—within the cell or from cell to cell—in a constant molecular chatter. I had not considered, however, that the genes in human tissues can also exchange information with the genes residing in the microbes that occupy our bodies. Cancer is a disease of information, of mixed-up cellular signaling. Now there is another realm to explore.

MUDDYING THE WATER

YET ANOTHER COMPLICATION has been uncovered by changes in our understanding of the biology of normal cells. For all their power to create and govern life, genes are made from combinations of just four nucleic acid letters: G, C, A and T. Each has a unique contour, and these patterns of bumps and grooves are copied from DNA to molecules known as messenger RNA and then ferried to the ribosomes, the cellular structures that use the information to make proteins. These proteins include the enzymes that help to make the genetic machinery run. The crowning simplification of the theory was what Francis Crick called the “central dogma”: DNA to RNA to protein.

The complications were soon to follow. Not every bit of DNA was part of the protein code. Some sequences were used for making the messenger RNA and transfer RNA. Others serve as control knobs, turning the volume of a gene up and down to modulate the production of its protein. With all of this intricate, interlocking machinery, you could almost entertain the fantasy that the whole thing was the product of an engineer. But nature was so much messier. Genes, for example, were not continuous. They were interrupted by scraps of gibberish. As the genetic message was reprinted into the messenger RNA, these blemishes—so-called introns—had to be edited out. They were accidents of evolution and of entropy. In fact, only a small percentage of the genome appeared to serve a purpose. The rest came to be known as junk DNA—a hodgepodge of genes that had become crippled and discarded over millions of years. With no compelling reason to get rid of the debris, it was carried along, generation by generation, for the ride.

It seemed barely conceivable that so much of the genome sat silent and inert. In its incessant tinkering, evolution would surely find new purposes for some of the discarded parts. Early in the 1990s scientists began to notice a new kind of RNA produced by the junk DNA. When they latched onto a messenger RNA, these molecules kept it from delivering its information.

Because of their small size, they were named microRNAs. They came in different varieties, and as they increased or decreased in number they regulated the production of various proteins. Like almost everything else in the cell, they were bound to play a role in cancer. Suppose there was a microRNA whose role was to block the expression of a growth-promoting oncogene. If the cell produced too little of this regulator, that would encourage proliferation. An excess of another kind of microRNA might result in the stifling of a tumor suppressor. In fact, just one of these molecules might regulate several different genes, leading to tangles of entwined effects. Mutations to the junk DNA had been thought to be harmless. But if they upset the balance of microRNAs, they could nudge a cell toward malignancy.

Junk that is not junk. Genes—99 percent of them—that reside in our microbes rather than in our own cells. Background seemed to be trading places with foreground, and I was reminded of what happened in cosmology when most of the universe turned out to be made of dark matter and dark energy. Yet for all the new elaborations, the big bang theory itself was left standing. It wasn’t so clean and simple as before, but it provided the broad strokes of the picture, a framework in which everything, aberrations and all, made sense.

The same appears to be happening with Hanahan and Weinberg’s six hallmarks of cancer. In March 2011, the two scientists wrote “Hallmarks of Cancer: The Next Generation.” Looking back on the decade that had elapsed since their paper, they concluded that the paradigm was stronger than ever. Certainly there were complications. Stem cells and epigenetics might come to play a greater role. In the end, there may be more than six hallmarks. The hope is that the number will be finite and reasonably small.

MORE TO EXPLORE


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Watch Douglas Hanahan talk about the six biological hallmarks of cancer—and perhaps one or two more—at ScientificAmerican.com/hov2013/cancer-hallmarks

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