The Genetic Basis of Human Cancer and Its Implications for Patient Management

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Forty years ago, cancer was a mysterious disease, with numerous theories invoked to explain its occurrence. Some thought it was caused by the breakdown of immunity as individuals age. Others believed that infectious agents such as viruses and bacteria were the major culprits. Another group of scientists hypothesized that it was caused by aberrant genes. And a competing theory posited that the genes in cancer cells were normal, but that they were expressed aberrantly.

As a result of world-wide efforts to understand the molecular basis of cancer since that time, cancer is no longer mysterious. We now know that cancer is, in essence, a genetic disease. In other words, it is driven by alterations in DNA that change the sequence or regulation of the genes that normally control cell birth and cell death - oncogenes and tumor suppressor genes, respectively. Oncogenes are like the accelerators in an automobile; a mutation in an oncogene is akin to having the pedal stuck to the floor. Tumor suppressor genes function like the brakes in an auto - a cell without its normal tumor suppressor genes is akin to an auto without brakes, impossible to control. In normal cells, the ratio between cell birth and cell death is exactly 1.00. If cell death exceeds cell birth, tissue atrophy results. If cell birth exceeds cell death because an oncogene or tumor suppressor gene is mutated, then a tumor results.

Cancers are notably different from other types of genetic diseases, such as muscular dystrophy or cystic fibrosis. Most diseases considered to be genetic are caused by inherited mutations. In cancers, the mutations are not generally inherited from the parents. Instead, most mutations develop after birth and occur in isolated, individual cells rather than in every cell in the body. A second major difference is that no single mutation „causes“ cancer. A sequential series of mutations is required for a clinically significant cancer to occur, each one leading to a greater ratio of cell birth to cell death.

Colorectal cancers provide an excellent example of the principles enumerated above. A colorectal tumor is initiated when a single, normal colorectal epithelial cell acquires a mutation in either the APC or β-catenin gene. This mutant cell gradually forms a microscopic tumor because its ratio of cell birth to cell death is higher than that of its surrounding non-mutant normal epithelial cells. One of the progeny of the mutant clone may eventually acquire a second mutation, such as one in the KRAS or BRAF genes. This now doubly mutant cell has an even greater selective advantage and can grow to a macroscopically visible size - a benign tumor called a polyp or adenoma. A third mutation, then a fourth, fifth, etc., in genes such as PIK3CA, p53, SMAD4, MRE11, FBXW7, occur by chance in successive generations. The resulting avalanche of mutations leads to tumor progression, culminating in invasive growth and metastasis from the primary site in the colon to the liver, lung, and other organs.

Colorectal cancers also illustrate another important concept relating genes to tumorigenesis. A small fraction of patients who develop colorectal cancers have a strong family history of the disease. There are two major forms of such hereditary predisposition, one called Familial Adenomatous Polpyposis (FAP) and the other called Hereditary Non-polyposis Colorectal Cancer (HNPCC). Patients with FAP inherit a mutant form of the APC gene and therefore develop hundreds to thousands of small polyps. But no single mutation is sufficient to engender cancer - it requires multiple mutations, as outlined above. Because there are so many polyps in FAP patients, however, at least one of them is likely to gradually acquire other mutations in KRAS, p53, PIK3CA, etc. and eventually progress to cancer.

HNPCC develops through a different route. These patients inherit a mutant form of an enzyme involved in repairing mistakes during DNA replication, a sort of spell-checking mechanism. HNPCC patients do not develop multiple polyps, but instead develop only one or a few, at the same frequency as the general population. But once a polyp is formed, the defect in repairing mistakes is revealed and the tumors acquire mutations in other genes - including oncogenes and tumor suppressor genes - in a relatively rapid fashion, so that tumorigenesis is accelerated. FAP can therefore be thought of as a disease of tumor initiation while HNPCC is a disease of tumor progression. Both initiation and tumor progression are required for a fully mature, lethal cancer to develop.

The last few years have witnessed further great strides in understanding the cancer genome. It has become possible to precisely identify the entire compendium of genes that are altered in a cancer. These studies have shown that colorectal cancers - like those of other common tumors such as breast, pancreas, and brain - have an average of ~70 gene-altering mutations. Roughly ten of these are in oncogenes or tumor suppressor genes, the others are „passengers" that have coincidentally occurred in the same cell that acquired a mutation in a „driver" cancer gene. Any two colorectal cancers, even though they may look the same under the microscope, have a different, overlapping set of mutations. This genetic variation explains much of the heterogeneity in the biologic properties of tumors and the differential responses of cancers to chemotherapeutic drugs and radiation.

Now that the basic landscape of the cancer genome is known, one of our major challenges is to figure out how to use this information to reduce morbidity and mortality from neoplasia. New therapies that target the mutant genes or the pathways through which these genes operate are being aggressively pursued in both industry and academia. But there is another route to achieving this goal that I believe will, in the final analysis, be equally important. Detailed studies of the temporal development of colorectal and pancreatic cancers have shown that it takes a long time - decades in fact - for a cell to accumulate all the mutations required to make it malignant. It is only in the last two or three years of this thirty-year journey that the tumor acquires the ability to travel outside its primary site, that is, to metastasize. And it is only in this last few years - once the tumor has metastasized - that a patient cannot be cured of his or her cancer through surgery alone. In essence, nearly every patient who dies from colorectal, pancreatic, or other solid tumors does so only because the presence of a cancer was not detected for the first twenty or thirty years of its existence.

The flip side of this observation is that the long development time provides a large window of opportunity for detecting incipient cancers while they are still curable by conventional surgical procedures. The new studies on the genomic landscapes of cancer are providing new opportunities for such early diagnosis. These opportunities include molecular imaging techniques that detect the abnormal pathways present in cancer cells through radioactive isotopes or non-radioactive probes. These abnormal pathways are also associated with changes in protein composition of the cancer cell, and some of these proteins leak into the circulation where they can in principle be detected by novel blood tests. A third opportunity involves detection of the mutant oncogenes and tumor suppressor genes themselves. These mutant sequences are the best possible biomarkers available; they are not simply associated with cancer - they are the proximate cause of cancer. Members of my laboratory have been attempting to detect these mutant genes in plasma and other bodily fluids in patients with cancer. Though these studies are still ongoing, it is already clear that circulating mutant genes can be detected in the great majority of patients with advanced disease and a significant fraction of patients with early-stage cancer.

The history of medicine shows that once a disease is understood, it is only a matter of time before suffering from that disease diminishes. That same history shows that for most diseases, the breakthroughs come from prevention rather than cure. In 50 years, cancer will not be the problem that it is today, in part because of improvements in therapy but even moreso because most cancers will either be prevented entirely or detected at a relatively early stage, when they can be managed by simply removing them with a scalpel.