# 101e Cancer Genetics

Pat J. Morin, Jeffrey M. Trent, Francis S. Collins, Bert Vogelstein

## CANCER IS A GENETIC DISEASE

Cancer arises through a series of somatic alterations in DNA that result in unrestrained cellular proliferation. Most of these alterations involve actual sequence changes in DNA (i.e., mutations). They may originate as a consequence of random replication errors, exposure to carcinogens (e.g., radiation), or faulty DNA repair processes. While most cancers arise sporadically, familial clustering of cancers occurs in certain families that carry a germline mutation in a cancer gene.

## HISTORICAL PERSPECTIVE

The idea that cancer progression is driven by sequential somatic mutations in specific genes has only gained general acceptance in the past 25 years. Before the advent of the microscope, cancer was believed to be composed of aggregates of mucus or other noncellular matter. By the middle of the nineteenth century, it became clear that tumors were masses of cells and that these cells arose from the normal cells of the tissue from which the cancer originated. However, the molecular basis for the uncontrolled proliferation of cancer cells was to remain a mystery for another century. During that time, a number of theories for the origin of cancer were postulated. The great biochemist Otto Warburg proposed the combustion theory of cancer, which stipulated that cancer was due to abnormal oxygen metabolism. In addition, some believed that all cancers were caused by viruses, and that cancer was in fact a contagious disease.

In the end, observations of cancer occurring in chimney sweeps, studies of x-rays, and the overwhelming data demonstrating cigarette smoke as a causative agent in lung cancer, together with Ames's work on chemical mutagenesis, provided convincing evidence that cancer originated through changes in DNA. Although the viral theory of cancer did not prove to be generally accurate (with the exception of human papillomaviruses, which can cause cervical and other cancers in human), the study of retroviruses led to the discovery of the first human *oncogenes* in the late 1970s. Soon after, the study of families with genetic predisposition to cancer was instrumental in the discovery of *tumor-suppressor genes*. The field that studies the type of mutations, as well as the consequence of these mutations in tumor cells, is now known as *cancer genetics*.

## THE CLONAL ORIGIN AND MULTISTEP NATURE OF CANCER

Nearly all cancers originate from a single cell; this clonal origin is a critical discriminating feature between neoplasia and hyperplasia.

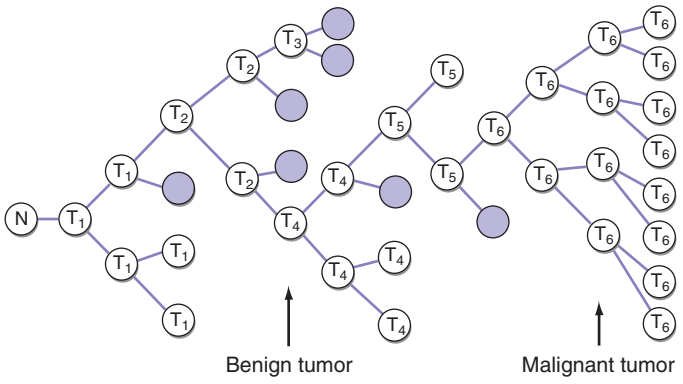


**FIGURE 101e-1 Multistep clonal development of malignancy.** In this diagram a series of five cumulative mutations ($T_1$, $T_2$, $T_4$, $T_5$, $T_6$), each with a modest growth advantage acting alone, eventually results in a malignant tumor. Note that not all such alterations result in progression; for example, the $T_3$ clone is a dead end. The actual number of cumulative mutations necessary to transform from the normal to the malignant state is unknown in most tumors. *(After P Nowell: Science 194:23, 1976, with permission.)*

Multiple cumulative mutational events are invariably required for the progression of a tumor from normal to fully malignant phenotype. The process can be seen as Darwinian microevolution in which, at each successive step, the mutated cells gain a growth advantage resulting in an increased representation relative to their neighbors (Fig. 101e-1). Based on observations of cancer frequency increases during aging, as well as molecular genetics work, it is believed that 5 to 10 accumulated mutations are necessary for a cell to progress from the normal to the fully malignant phenotype.

We are beginning to understand the precise nature of the genetic alterations responsible for some malignancies and to get a sense of the order in which they occur. The best-studied example is colon cancer, in which analyses of DNA from tissues extending from normal colon epithelium through adenoma to carcinoma have identified some of the genes mutated in the process (Fig. 101e-2). Other malignancies are believed to progress in a similar stepwise fashion, although the order and identity of genes affected may be different.

## TWO TYPES OF CANCER GENES: ONCOGENES AND TUMOR-SUPPRESSOR GENES

There are two major types of cancer genes. The first type comprises genes that positively influence tumor formation and are known as *oncogenes*. The second type of cancer genes negatively impact tumor growth and have been named *tumor-suppressor genes*. Both oncogenes and tumor-suppressor genes exert their effects on tumor growth

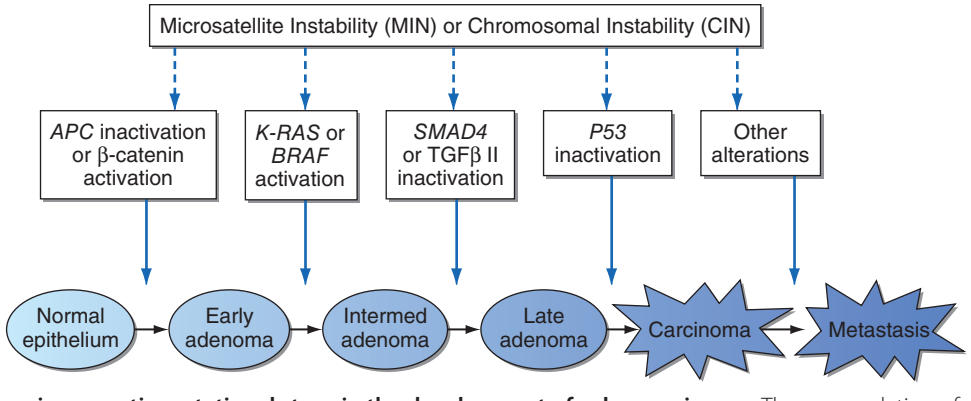


**FIGURE 101e-2 Progressive somatic mutational steps in the development of colon carcinoma.** The accumulation of alterations in a number of different genes results in the progression from normal epithelium through adenoma to full-blown carcinoma. Genetic instability (microsatellite or chromosomal) accelerates the progression by increasing the likelihood of mutation at each step. Patients with familial polyposis are already one step into this pathway, because they inherit a germline alteration of the *APC* gene. TGF, transforming growth factor.