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The Genetic Basis of Cancer

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1. INTRODUCTION

Cancer is a genetic disease in which malignant cells have undergone mutations and epigenetic changes but maintain the transformed phenotype even when cultured or when injected into immunologically tolerant experimental animals *(1,2)*. However, most of the genetic events in tumors are somatic (i.e., not hereditary), brought about environmentally or randomly, and the identified inherited (often referred to as "genetic") causes account for a small proportion of all cancers.

Specifically, the genes with mutations that are relevant to the carcinogenic process, fall into two classes: tumor suppressor genes and oncogenes. The distinction between heritable and environmental causes may be easily made if a hereditary cancer syndrome or an environmental exposure, such as tobacco smoking or human papilloma virus, poses a high risk. For most common cancers, this is not the case, and they are therefore considered complex diseases caused by many underlying and interacting genetic and environmental factors. Heritable effects would lead to a clustering of cancer in families *(3,4)*. However, familial clustering can also be caused by shared environment or lifestyle, and an increased familial risk does not tell whether the reason is heritable or environmental *(5)*.

In this chapter, we discuss causes of cancer and the underlying molecular mechanisms from the point of view of potential gene therapy approaches. Improved understanding of the causes of cancer will be helpful for scientific, clinical, and cancer preventive measures. A certain notion of cancer causation, often implicit, is embedded in many science and health policy decisions.

2. THE GENETIC BACKGROUND OF CARCINOGENESIS

In a nutshell, cancer can be considered a disease caused by mutations and epigenetic changes (e.g., methylation defects) in tumor suppressor genes and oncogenes *(6)*. Mutations may be the more common of the two types of changes and can be missense (altered amino acid), frameshift (altered reading frame), or nonsense (truncation of protein product). Sometimes, mutations do not affect the amino acid sequence, but rather influence the promoter or splice sites. Deoxyribonucleic acid (DNA) sequence variations that do not have a direct unequivocal link to the phenotype of interest but may play a role are called *polymorphisms*.

There are various mechanisms that can cause mutations. These include deletions of small or large DNA segments, inversions, translocations, looping leading to truncated sequence, and so on. The initial causes for these mechanisms range from ultraviolet radiation to chemical and viral carcinogens, but for most cases of cancer, causation remains poorly defined. Probably, diet and other environmental causes play a major role, but cause–effect relationships are difficult to demonstrate conclusively because of the long time between initiation of a tumor and clinical presentation. Hereditary mutations have also been identified as a cause of cancer and are discussed here.

From: *Contemporary Cancer Research*
Cancer Gene Therapy
Edited by: D. T. Curiel and J. T. Douglas © Humana Press Inc., Totowa, NJ

By definition, genetic changes important for carcinogenesis (i.e., can be detected as clonal changes in malignant tumors) inactivate tumor suppressor genes or activate oncogenes. Both groups include dozens of well-defined members, and hundreds probably remain poorly characterized. A classic example of an oncogene is *RAS*, which was initially identified as a gene activated in the process of virally induced tumorigenesis. Later, mutations of *RAS* have been commonly found in a wide variety of cancers. Most protein products of oncogenes are involved in signal transduction and growth regulation. An activating mutation of one allele is usually sufficient.

The normal functions of proteins coded by tumor suppressor genes are often related to important regulatory or housekeeping functions crucial to the integrity of cellular functions, including cell division and programmed cell death. Therefore, the loss of these functions is beneficial to malignant progression. In most cases, both alleles of a tumor suppressor gene must be lost for loss of function of the protein product. Often, one allele is lost because of a "local" mutation; the other allele is lost because of a large deletion (loss of heterozygosity). Classic tumor suppressor genes include *p53* and *APC* (adenomatous polyposis *coli*). The former has a wide variety of functions associated with cell cycle control and programmed cell death (apoptosis). Mutations of *p53* have been identified in more than half of all cancers.

APC was initially identified as the gene harboring germline mutations in patients with familial adenomatous polyposis, a hereditary disorder that leads to formation of hundreds of intestinal polyps that, when untreated, eventually undergo malignant transformation and cause death at a young age. *APC* has multiple functions involved with cellular signaling and adhesion. The *APC* example is interesting for two reasons. First, it is a useful example of a rare genetic disorder revealing the molecular background of common disease. Although familial adenomatous polyposis is rare, mutations of *APC* (or members of its signaling pathway) were consecutively identified in virtually all colorectal cancers. In fact, the same is true for most of the cancer syndromes discussed in this chapter. Although the syndromes are rare, the causative genes are commonly involved in sporadic carcinogenesis as well.

Second, studies (many of which were performed by Bert Vogelstein and colleagues at Johns Hopkins in Baltimore, MD) of *APC* and the genetic basis of colorectal cancer have revealed another aspect that may be common for many types of malignant tumors. Inactivation of *APC* may be the initial or an early step in many colorectal cancers, but it is not the only change found in advanced tumors. Instead, carcinogenesis may often be a multistep process in which additional mutations confer features useful for increased growth and decreased susceptibility to growth regulation (Fig. 1).

It is unlikely that all occurring mutations are beneficial to the malignant clone. Instead, the majority may give rise to subclones that have reduced viability or perhaps increased detection by the immune system. Nevertheless, the rare beneficial changes gain a growth advantage and can thus be detected in the end product of the multistep process of carcinogenesis, which in most cases is an aggressively growing tumor capable of invasion and metastasis.

The gene that sustains the initial mutation that allows the carcinogenic process to proceed has been called the gatekeeper gene (Gene 1 in Fig. 1). The theory is that each cell type may have a crucial growth regulatory circuit; its inactivation may be necessary for carcinogenesis. For example, *APC* has been suggested as the gatekeeper for the colorectal epithelium. Another suggested class of tumor suppressor genes is the caretaker genes; their inactivation may facilitate the multistep process of carcinogenesis by allowing rapid accumulation of further mutations *(2)*. These genes are often involved with DNA repair and maintaining the integrity of the genome.

For gene therapists, an important question is how many steps of the multistep process need to be blocked for effective intervention? Presently, the complete answer is not known. Nevertheless, most available evidence suggests that correction of a single defect, such as replacement of a defective tumor suppressor gene or inactivation of an overactive oncogene, can be sufficient for controlling the malignant process. For example, when *p53* is expressed in *p53* mutant cancer cells (with many other mutations as well), the cells undergo apoptosis and may in fact trigger neighboring cancer cells to do the same.

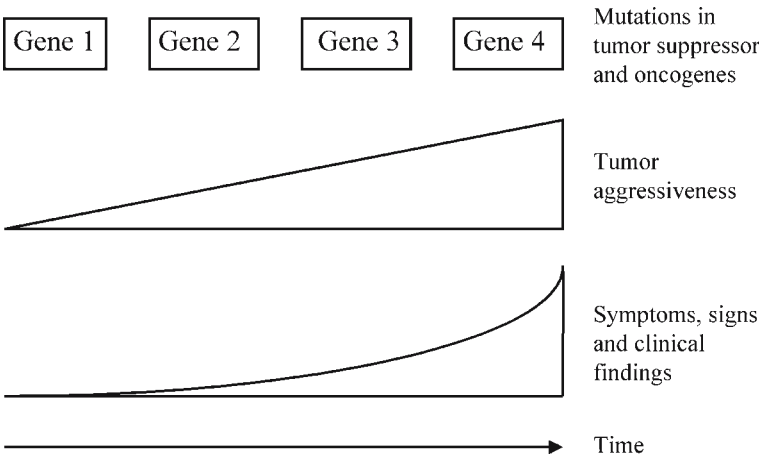

Fig. 1. The multistep nature of cancer. Mutations accumulating in tumor suppressor genes and oncogenes result in increasingly aggressive behavior, that is, the capacity for invasion and metastasis. Together with increasing size, these features usually eventually result in clinical symptoms and findings. Most organs and body compartments have significant reserve capacity; therefore, symptoms often arise late in the evolution of the tumor.

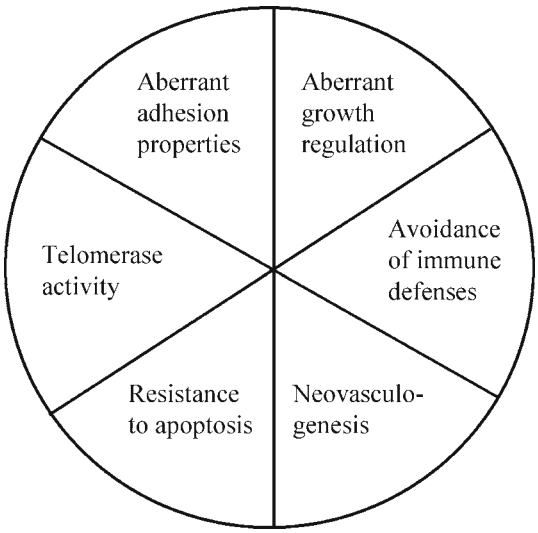

Fig. 2. Common features of advanced cancers.

Thus, perhaps the malignant phenotype can be compared to a house of cards, for which removal of any card causes the whole structure to collapse. This is not completely surprising considering the various defenses the human body has against malignant cells. Fittingly, malignant cells can be detected circulating in healthy individuals who never develop cancer. Further, cancer typically arises in advanced age, when the body's defense mechanisms have slowed, but the cancer has had decades to develop a delicately balanced combination of features that allow sustained growth while remaining undetected by the immune system.

An increasing number of genes are identified as tumor suppressor and oncogenes, and the respective protein products seem to have a wide variety of functions *(1,6)*. Nevertheless, many cancer-associated genetic changes seem to fall into six categories (Fig. 2), which include (1) aberrant adhesion

Table 1
Heritable Effects of Cancer and Some Involved Genes

	Proportion of variance attributed to heritable effects		
Cancer site	From twins	From families	Known genes
Stomach	0.28	0.01[a]	E-cadherin
Colorectum	0.35[a]	0.13[a]	Mismatch repair, *APC, LKB1*
Pancreas	0.36	—	*CDKN2A*
Lung	0.26	0.08[a]	Metabolic low-penetrance genes
Breast	0.27[a]	0.25[a]	*BRCA1/2, ATM* (ataxia telangiectasia mutated)
Cervix uteri	0	0.22[a]	Immune response genes?
Corpus uteri	0	—	Mismatch repair, *PTEN*
Ovary	0.22	—	*BRCA1/2*, mismatch repair
Prostate	0.42[a]	—	Candidate loci
Bladder	0.31	0.07[a]	Metabolic low-penetrance genes
Leukemia	0.21	0.09[a]	*ATM*, helicase

Source: Based on a Nordic twin *(7)* and a Swedish family study *(8)*.
[a]95% confidence interval does not include 0.0; that is, the estimate is statistically significant.

properties (e.g., loss of contact inhibition), (2) exaggerated or unphysiological response to growth-promoting signals and reduced responsiveness to growth-regulating signals, (3) failure to undergo programmed cell death on genetic damage (dysfunction of cell cycle checkpoints), (4) immortalization (gain of telomerase activity), (5) avoidance of immune defenses, and (6) factors promoting neovasculogenesis (rapidly growing tumors need an ample supply of oxygen and nutrients). Importantly, all of these features are distinct from characteristics found in most nonmalignant cells and thus may allow intervention.

3. APPORTIONING CANCER CAUSATION

Although most cases of cancer are somatic, that is, they do not have an identifiable familial component, studies of hereditary syndromes have produced or initiated much of today's understanding of cancer as a genetic disease. It is not unreasonable to assume that this will be true in the future as well; therefore, we briefly discuss hereditary cancer here.

Two studies have provided unique insight into the familial component of various common cancers. The first study used the classic twin design, that is, comparison of correlation of cancer in monozygotic and dizygotic twins from three Nordic countries *(7)*. In this model, it is assumed that both types of twins equally share the environmental effects; monozygotic twins are genetically identical, whereas dizygotic twins are like any siblings, sharing by average 50% of their genes. The second study was based on the nationwide Swedish Family-Cancer Database of 3 million families *(8)*. It compared correlation of cancers between all family members using the same statistical model used in the twin study. It had a much higher statistical power than the twin study because the whole Swedish population and its 1 million tumors were scrutinized. On the other hand, most sex-specific cancers could not be assessed in the model.

The results from both models are presented in Table 1. For stomach cancer, heritability was estimated to account for 28% from the twin study and 1% from the family study. The remainder, 72% and 99%, respectively, could be the total environmental effect, of which the majority were because of nonshared or random environment. The twin study gave statistically significant heritability estimates (for which the 95 % confidence interval did not include zero) only for cancers of the colorectum (35%), breast (27%), and prostate (42%). The family study gave an identical estimate for the breast, but a lower estimate for the colorectum. The heritability of cervical cancer was 22%, but that of lung and bladder cancer and leukemia was less than 10%.

Caution should be used in overinterpreting these estimates from statistical modeling. However, certain common cancers showed a much higher range of heritability than that observed by comparing familial risks between first-degree relatives *(9)*. If the estimates for colorectal, breast, and prostate cancers, showing 27–42% heritability, are confirmed, there are major gaps in the understanding of the genetic basis of these neoplasms.

Some of the genes that transmit familial risks are indicated in Table 1 *(2)*. The frequencies of mutations in the well-known high-risk susceptibility genes *BRCA1* and *BRCA2* in breast cancer and DNA mismatch repair genes in hereditary nonpolyposis colorectal cancer (HNPCC) are so low that they explain at most 10% of the heritability noted, and 90% remain unaccounted *(10,11)*. For prostate cancer, candidate genes have been mapped, but not identified *(12–16)*. These findings suggest that other genes are yet to be identified, but because their polymorphisms are likely to be relatively common and confer only a modest risk increase, their identification will be difficult.

4. CANCER MODELS

Well-characterized cancer syndromes, such as familial retinoblastoma, *BRCA*-linked breast cancer, and HNPCC, follow a dominant Mendelian pattern of inheritance, with high penetrance (proportion of genotype carriers with phenotype); therefore, close to 50% of the offspring of an affected parent present with the disease. Nevertheless, these syndromes are rare, and the frequency of the mutant gene is on the order of 1/1000 (carrier frequency = 1/500) or less. The most common cancer syndromes *BRCA1* and *BRCA2* and HNPCC are thought to account for 1–3% all breast and colorectal cancers, respectively *(10,17,18)*. Bloom syndrome, ataxia telangiectasia, and xeroderma pigmentosum are examples of Mendelian recessive cancer syndromes. About 25% of the offspring of two heterozygote parents display symptoms, including neoplasms. It is relatively easy to estimate the proportion of all cancer because of such well-characterized monogenic syndromes conferring a high risk, and 1% appears to be a good estimate *(19)*.

Most common cancers are caused by alterations in many genes. According to the multistage theory of cancer, the clonal tumor emerges as a result of a number of mutations in a single cell *(20–27)*. The first mutations occur in normal cells, creating a slow-growing preneoplastic colony. Additional changes in a cell of the preneoplastic colony are believed to be necessary to create a neoplastic cell capable of growing as a malignant tumor. The number of required mutations may vary and probably depends on the genes and cell types affected. This is probably true for cases arising as a result of hereditary mutations as well. The initial gatekeeper mutation may confer a growth advantage and thus increase the target size (number of cells with the initiating defect) for subsequent promotional mutations. Mathematical adoption of known mutation rates, number of stem cells, and normal human life-span can accommodate a carcinogenic process with three or more mutations, such as two in the initiation stage and one or more in the promotional stage *(24,25)*.

When two or more genes are involved, it is difficult to observe Mendelian inheritance in pedigrees *(27)* because the likelihood decreases that an offspring will inherit the parental set of disease genes. Therefore, it is difficult to distinguish multifactorial inheritance from low-penetrance single-gene or environmental effects, which is a major challenge to current segregation analyses *(28–30)*. In the twin model, polygenic inheritance would be expressed as a much higher risk among monozygotic than dizygotic twins *(3,31)*. Another model in which polygenic inheritance could be distinguished is in multiple primary cancers in the same individual *(32,33)*.

5. CANCER GENES

Only a small proportion of cancer is because of single-gene, dominant traits *(6,34)*. However, the affected families have been helpful in the efforts of gene identification, and the majority of the tumor-related high-penetrance genes have been described from such families *(2)*. Results can be obtained even for rare cancer syndromes, such as Peutz-Jeghers or skin and uterine leiomyomas if the families

are homogeneous and the risk is high *(35,36)*. An interesting aspect of the leiomyoma study was that the gene turned out to be fumarate hydratase coding for an enzyme in the tricarboxylic acid cycle. Another enzyme in this metabolic pathway, succinate dehydrogenase, was implicated in hereditary paragangiomas and pheochromocytomas *(37)*. These data have widened the scope of tumor-related genes to metabolic, housekeeping genes from the earlier cell cycle regulator, DNA repair, and signal transduction paradigms.

5.1. High-Risk, Rare Genes

Many forms of cancer in which a single gene poses a high risk have been identified. Of the 4700 dominant and 2800 recessive human genetic traits known in the early 1990s *(31)*, some 440 were single-gene traits in which cancer was a complication; many of them were extremely rare, with a few identified families worldwide *(38)*. Most known cancer syndromes are dominant at the population level (although recessive at the molecular level; *19*), the gene carriers are type Aa, where a = mutant gene. In tumors, the normal allele is lost (loss of heterozygosity), and the tumor is therefore hemizygous a or homozygous aa if another mutation occurs instead of allele loss. In dominant cancer syndromes, the penetrance is typically high, often approaching 100%, which facilitates identification of the dominant pattern because cases are found in all generations.

Some rare cancer syndromes, such as xeroderma pigmentosum, ataxia telangiectasia, and Bloom syndrome, are recessive (aa) at both population and molecular levels. The detection of recessive conditions is difficult because the cases appear apparently randomly in pedigrees, but often reveal consanguinity at a closer inspection. Population geneticists have raised questions about the relatively small number of known human recessive syndromes. In species of experimental animals, recessive traits predominate, as opposed to humans, for whom dominant traits are more common *(31)*. It is not excluded that this is an observation bias because of difficulties in identifying a recessive pattern. A further complication is that, in many cancer syndromes, the mutations are *de novo* germline mutations lacking familial pattern. This is the case for most disorders for which cancer occurs early; thus, the propagation of the defect to further generations is reduced. Examples include Wilms tumor, retinoblastoma, and neurofibromatoses 1 and 2 *(39)*.

The relative risks (RRs) of cancer may be very high (<1000) in the rare cancer syndromes. In fact, if the penetrance is close to 100%, RR depends on the population frequency of the disease only. Most known syndromes affect young individuals, for which the population incidence is low, resulting in excessive RRs. The unusual risk of rare cancers in young individuals has facilitated identification of syndromes, including Li-Fraumeni, multiple endocrine neoplasia 2 (MEN2), and HNPCC *(40,41)*. The RR of childhood cancers in Li-Fraumeni syndrome (hereditary *p53* mutation) has been estimated at >100 *(42)* and that of colorectal cancer in HNPCC at 70 *(17)*. The estimates from the Swedish Family-Cancer Database give RRs of 30 for endometrial cancer in HNPCC and 5000 for medullary thyroid cancer in MEN2 *(43,44)*.

The proportion of gene carriers depends on the population, and the most accurate estimates are available for Europeans and European Americans. Among the known dominant cancer syndromes, the frequency of gene carriers is highest for HNPCC, about 1/500, and BRCA1 and BRCA2, each about 1/1000. For most others, such as Li-Fraumeni, MEN1 and 2, neurofibromatosis 1 and hereditary renal cell cancer (caused by mutation in VHL), retinoblastoma, Wilms, and Gorlin cancers, the frequency of carriers ranges from 1/3000 to 1/50,000 *(39)*. In recessive conditions, such as xeroderma pigmentosum and ataxia telangiectasia, the frequency of diseased (a^2) is low (1/1 million and 1/40,000, respectively), but the carrier frequency (2Aa) of ataxia telangiectasia has been estimated at 1–5% in the US population *(45)*. If heterozygotes are at risk for cancer, the impact may be significant. Ataxia telangiectasia heterozygotes may have an elevated risk of various cancers, such as breast cancer, and because of the large number of carriers, calculations argue that the attributable proportion of ataxia telangiectasia in breast cancer is higher than that of *BRCA1* and *BRCA2 (46,47)*.

A further aspect of familial cancer syndromes is that they often affect cancers at multiple sites, even though detected through cancers at a particular "index" site. Li-Fraumeni syndrome is an example, with more than a 100-fold RR at the index sites (childhood sarcomas), but a modest RR for more common diseases such as breast cancer. Further examples are HNPCC, *BRCA1*, and *BRCA2*. In the recessive cancer syndromes, including ataxia telangiectasia and Bloom, the affected individuals can present with almost any kind of malignancy *(45,48)*.

Another aspect relating to the identification of a clinical entity is the presentation of other diseases in many of the known syndromes. Patients with recessive cancer syndromes are severely handicapped, as indicated by some of their descriptive names. Severe noncancer diseases beset even dominant conditions such as NF1 and NF2, MEN 1 and 2, and hereditary renal cell cancer.

5.2. Low-Risk, Common Genes

Familial effects in cancer are not only because of high-risk gene defects as discussed previously, but most likely there is contribution by more common low-risk defects, which may be frequent enough to be called polymorphisms (sometimes defined as the variant present in more than 1% of the population). Many polymorphisms have been described in the areas of drug and carcinogen metabolism, with some recent data also on hormone receptors and DNA repair genes *(49–51)*. Although it is likely that a large number of low-risk genes modulate the carcinogenic process in humans, there has been much controversy in the current literature on the role of metabolism genes in cancer *(52)*.

Immune surveillance plays an important role in cancer, as has been observed in immunosuppressed patients who are at a marked risk of lymphomas and many types of squamous cell carcinomas *(53,54)*. Milder forms of immunodeficiencies probably explain some familial patterns of non-Hodgkin's lymphoma, Hodgkin's disease, cervical cancer, and squamous cell skin cancer *(53,55,56)*. Suppressed immune function is also likely to modulate host response to virus, such as human papilloma virus and Epstein-Barr virus *(57–60)*.

6. CONCLUSION

There are no data available on the etiology of cancer that would refute the predominant role of environment as a causative factor. However, since the epochal review by Doll and Peto in 1981 *(61)*, disappointingly little progress has been seen in the search for new causes of environmental carcinogenesis. One likely reason is that environmental carcinogenesis is because of the interaction of external and host factors, which cannot be unraveled by epidemiological or molecular biological means alone. There is hope that merging of these approaches into molecular epidemiology or, even better, into molecular genetic epidemiology will tool the exogenous/endogenous interphase of human carcinogenesis. Nevertheless, there is little doubt that, regardless of the causative agents, on the molecular level the malignant process manifests as mutations and epigenetic changes in tumor suppressor and oncogenes. Further, the accumulation of mutations in these genes gradually increases the aggressiveness of the clone and therefore constitutes the multistep process of carcinogenesis.

All the main types of cancer appear to have a familial component with a frequency that varies, but often ranges from 1 to 5%. Familial risks observed among twins and among patients with multiple primary cancers provide support for the multistage carcinogenesis in human cancers at a population level *(27,30)*. There are at least three practical implications from such findings. One is that, in the search for new susceptibility factors in cancer, low-penetrance genes may be better identified in association studies with a case–control design than in linkage studies *(62–64)*. The second implication is that, in clinical counseling, polygenic and recessive conditions imply uncertainty *(30)*. The disease strikes apparently randomly even though there is an inherited background.

The third problem that may have implications for gene therapy approaches involves a question: If many genes contribute to each case of cancer, is blocking or repair of one defect sufficient for reverting the malignant phenotype? Current evidence suggests that removing one "card" (mutation) from

the "house of cards" (advanced malignant tumor) can be enough. Nevertheless, considering the awesome capacity of cancers to acquire resistance, a cytostatic effect may not be desirable, and rapid killing of cells may be required instead. In addition to resistance on the cellular level, tumors can acquire resistance on the tissue level. This implies the existence of subclones that are not sensitive to the treatment. Therefore, removing multiple cards simultaneously or consecutively could have advantages.

Identification of cancer as a disease caused by mutations and epigenetic changes in genes immediately suggested gene therapy as a logical means for intervention. Thus, if the causative defects can be corrected or blocked, the disease phenotype can be reversed. Alternatively, the genetic changes present in cancer cells offer a variety of characteristics that separate them from noncancer cells. These features include dysregulated promoters and enhancers, aberrant expression of receptors and epitopes, and loss of antiviral defense mechanisms. As discussed in this book, these features can be utilized in the planning of gene therapy strategies aimed at direct killing of cancer cells.

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