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Origin, Evolution, and Regulation of Cancer Genes: An Overview

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Abstract

Cancer is characterized by abnormal cell proliferation in multicellular organisms. Its emergence is linked to the evolution of multicellularity billions of years ago. The "incipient cancer genes" (proto-oncogenes) presumably evolved from genes involved in cell reproduction during the evolutionary transition from unicellular to multicellular organisms. Although these incipient cancer genes initially promoted rapid cell division required for growth at specific developmental stages, their activity had to be tightly regulated to ensure balanced growth and differentiation during evolution. Genes that restrain proto-oncogene activity are known as tumor suppressor genes (TSGs). Cancer is a multistep process involving multiple genes. In this review, human cancer is considered within the framework of a two-phase genetic model of carcinogenesis: initiation and development. In the two-phase model, the initiation phase may require as few as two, or at most a small number of, genetic alterations (such as gene mutations or chromosomal abnormalities). This phase is potentially irreversible. The developmental phase may involve two or more genetic and/or epigenetic alterations. If it involves epigenetic changes, the developmental phase may be reversible. In this proposed model, key changes primarily affect tissue-specific tumor suppressor genes. The number of such regulatory tumor suppressor genes (*TS*-genes) may vary across tissues. Diverse environmental factors such as chemical carcinogens, ionizing radiation, and viruses, acting singly or in combination, may impair the function of tumor suppressor genes either directly or indirectly through mutational or epigenetic mechanisms, thereby contributing to the initiation and development of cancer. This model accounts for both hereditary and sporadic human cancers. Spontaneous or induced regression of tumor cells to the normal state may be centered on the developmental phase of carcinogenesis. This review proposes that the origin of cancer genes is integral to the evolutionary history of multicellular organisms.

Keywords:

cancer genes; evolution of cancer genes; origin of cancer genes; tumor suppressor gene; mutations; genetic-epigenetic regulation

1. Introduction

1.1. The Premise-Historical Perspective

Cancer is a disease of living cells in multicellular organisms, and as long as there are living cells capable of division, there exists the possibility that they may become cancerous. This may be regarded as the fundamental principle governing cellular behavior! The origin and evolution of cancer cells can be traced back to the origin of life billions of years ago. This review suggests that the origin of cancer genes is closely linked to the evolutionary history of multicellular organisms. It is likely that life originated on Earth between 3 and 3.8 billion years ago [1]. The origin of self-replicating molecules, whether autocatalytic protein polymers [2], RNA, or DNA, was crucial for the development and evolution of life on Earth. The initial molecular systems could, in principle, both reproduce and

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evolve without having a Mendelian genome [2]. However, unicellular or multicellular systems require a genome for growth, differentiation, and evolution. In such systems, DNA serves as the primary genetic material. Although the genetic code contains only four letters, A (adenine), C (cytosine), G (guanine), and T (thymine), the arrangement of these letters provides enormous potential for genetic variation and the origin of species. The earliest pre-life forms may have consisted of simple RNA or DNA molecules capable of surviving in Earth's early hostile environment.

As life evolved from unicellular to multicellular forms, three-dimensional growth and differentiation became essential processes, alongside cell reproduction, for the further development and evolution of higher forms of life. It is proposed that ancient "incipient cancer genes" (proto-oncogenes) evolved in retroviruses and were later incorporated into multicellular organisms during evolution [3]. Although initially these proto-oncogenes were involved in rapid cell division required at specific developmental stages, their activity had to be regulated for balanced growth and differentiation. Another set of genes, known as tumor suppressor genes, evolved to regulate proto-oncogenes by controlling their activity. Thus, two types of cancer-related genes, tumor suppressor genes and proto-oncogenes, coexist in the genomes of multicellular organisms, including humans.

More than 100 years ago, when Peyton Rous [4] showed that a filterable agent isolated from the sarcoma, known as Rous sarcoma virus (RSV), of the chicken breast was transmissible to other chickens, thereby showing that some cancers have an infectious etiology. This led to the discovery of oncogenes and paved the way for subsequent research in cancer molecular biology and medicine. In addition, several animal model systems have been used to investigate the role of oncogenes in human cancer. These include pigs, Drosophila, genetically engineered mice, zebrafish, cancer cell lines [5,6], and Xiphophorus fish [7,8].

2. Cancer Origin and Regulation

On average, the adult human male body consists of approximately 36 trillion cells, whereas the adult female body consists of about 28 trillion cells [9]. There are over 400 cell types, including 145 types of neurons, in the human body [9,10]. The precise number of cancer-associated genes in humans remains uncertain. Nevertheless, current estimates of cancer genes range from 70 genes associated with germline mutations and 342 genes associated with somatic mutations [11]. Another study has listed 727 known cancer genes [12]. Since there are differences in the incidence of cancer across tissues/organs, it may be postulated that cancer genes in different organs are regulated by different sets of tissue-specific regulatory/tumor suppressor genes. The regulatory tumor suppressor (*R*) genes may be linked and/or unlinked to tumor (*Tu*) genes. Mutation of the *R* genes, or impairment of their function by radiation, chemical carcinogens, or environmental factors, would release the *Tu* from the restraint and trigger a chain of events which may lead to the development of tissue-specific neoplasms [13,14].

Recent genetic theories of cancer have invoked the concept that sites of mutations are the regulatory (*R*) genes [13,14], or anti-oncogenes (*anti-onc*) [15], or tumor suppressor (*TS*) genes [16,17] that normally control the expression of genetic information, which, when uncontrolled, would lead to neoplastic development. Such genetic information seems to be encoded by the structural genes, the so-called transforming (*Tr*) genes [18] or tumor (*Tu*) genes [13,14], or cellular oncogenes (*c-onc*) [19–21], and some of these genes may be tissue-specific. The regulatory genes (*R*-genes/*TS* genes) may be linked to or unlinked from the oncogenes. Elimination of R-genes or impairment of their function by radiation, chemical carcinogens, or viruses can release oncogenes from regulatory control and initiate a cascade of events that may lead to the development of tissue-specific neoplasms [13,14]. Cancer initiation and development occur in multiple stages. Following the initiation phase, the initial cell undergoes primary changes that make it neoplastic. Subsequent mutations may promote clonal selection, ultimately leading to neoplastic development. In other words, carcinogenesis involves both tumor initiation and the clonal evolution of tumor cells [22,23]. For clarity, cancer genes or oncogenes are denoted as *Tu* (tumor genes), and their regulatory counterparts are denoted as *TS* (tumor suppressor genes) throughout the remainder of the text.

For the purposes of discussion in this paper, we shall mainly focus on the *Tu* genes in hereditary and non-hereditary cancers. The precise function of these genes remains conjectural. However, it seems likely that these potentially cancer-causing genes are transiently active at different stages of embryonic development or during cellular repair. Those genes that accomplish the necessary regulation and restraint of this potentially tumor-inducing information, previously designated as regulatory genes [13,14], are the tumor suppressor (*TS*) genes [16,17], and their location as *TS* loci [24]. These loci are specific to a given tissue or cell type, and the number of such loci differs for different tissues. Mutation of *TS*-genes or impairment of *TS*-gene function by environmental carcinogens, such as chemical carcinogens or radiation, would release cancer genes from normal constraints and may lead to the development of neoplasms [13,14].

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Tumor suppressor genes play a crucial role in the development of a wide range of human cancers and can be influenced by environmental factors. The molecular mechanisms underlying variation in tumor suppressor genes may involve genetic changes at different genomic locations, depending on the tissue/organ type. Future research in molecular genetics may offer further insights into these questions.

Proto-oncogene activation and tumor suppressor gene inactivation synergistically promote cancer and constitute a target group in neoplastic cells. It is speculated that the proto-oncogene might be first activated to the state before the tumor suppressor genes are inactivated. However, additional evidence is required to support this hypothesis.

3. Genetic Change and Cancer

It has been estimated that more than 75 percent of human cancers are attributable to environmental factors, such as cigarette smoke, asbestos, chemical carcinogens, ultraviolet radiation, and X-rays [25–28]. Viruses have also been implicated in the etiology of some human cancers [29–31]. Although the precise mechanisms by which a normal cell becomes a cancer cell are not yet fully understood, it seems likely that these diverse environmental factors, singly or in combination, may affect the cell's genetic components. They may impair tumor suppressor (TS) genes by causing genetic changes (gene mutations, chromosomal aberrations, or genetic transpositions) [32,33], or by inducing epigenetic (developmental) changes [34,35].

The concept of cancer mutation dates back to the beginning of the present century, when Theodore Boveri published a classic book titled "Zur Frage der Entstehung maligner Tumoren" (On the Origin of Malignant Tumors) in 1914 [36]. Based on his detailed observations in cell biology, Boveri concluded that: (1) tumor cells are derived from normal cells, with the causes of abnormalities inherent to the tumor cells, and (2) cells of malignant tumors possess a cellular defect, having lost part of their normal cellular components. Boveri further postulated that the abnormal morphology of chromosomes (in particular chromatin complex) frequently observed in tumor cells was central to the origin of tumors. Boveri's concept of the abnormal chromatin complex in tumor cells, later known as the somatic mutation theory of cancer, has been widely discussed in relation to physical and chemical carcinogenesis. However, the way mutations drive malignancy remains enigmatic. Carcinogens interact with DNA and cause damage. If this damage is not properly repaired, it becomes fixed as a mutation in the replicating DNA molecule. Mutations affecting genes directly or indirectly involved in regulating cell reproduction and differentiation may lead to neoplastic development.

Environmental factors can affect the function of tumor suppressor genes. However, environmental factors may induce methylation of tumor suppressor genes. Carcinogens in cigarette smoke, along with other harmful environmental factors, cause extensive DNA damage and genomic alterations.

4. Epigenetics in Cancer Development

The word epigenetics was introduced by the British embryologist Conrad Waddington in 1942, who defined it as "the branch of biology which studies the causal interaction between genes and their products, which bring the phenotype into being" [37]. Tumor suppressor genes play a crucial role in the development of a large array of human cancers. The molecular mechanisms underlying variation in tumor suppressor genes may involve alterations at different genomic loci, depending on the tissue/organ type. Future research in molecular genetics may provide more insight into these questions.

Epigenetics involves changes in gene activity through the silencing or modification of gene expression, without altering the underlying gene structure through mutations. The three primary mechanisms for epigenetic changes are "(1) DNA methylation, (2) histone modification, and (3) non-coding RNA-associated gene silencing" [38]. The developmental or differentiation theory suggests that cancer may arise without primary mutational events; it could result from epigenetic changes [38–42]. Epigenetic transcriptional mechanisms, together with the unlocking of phenotypic plasticity during tumor evolution, play a crucial role in cancer development [43,44]. The prevailing view is that development and differentiation result from epigenetically controlled changes in gene expression, rather than from changes in the structure of genetic material. Similarly, cancer, characterized by defective differentiation, may result from epigenetic changes [45] in gene expression rather than from mutations in the primary structure of genes. Therefore, cancer would be potentially reversible [46–49] in the sense that differentiation may be reversible. The epigenetics hypothesis does not rely on the presence of specific cancer genes. Instead, it proposes that certain tissue-specific epigenetic genes, which normally regulate cell reproduction and tissue differentiation, may, when mis-programmed, lead to neoplastic development [50]. However, more recently, it also considers cancer-promoting genes (or cellular oncogenes) as potential epigenetic targets [51,52]. Regardless of the

cancer epigenetics hypothesis, there is a probability of interaction between mutational and developmental events in cancer development.

Epigenetic mechanisms play a crucial role in normal development and in the regulation of tissue-specific gene expression patterns. The primary mechanisms involved in epigenetic gene silencing include DNA methylation.

5. A Genetic/Epigenetic Concept of Cancer

It is suggested that genetic and epigenetic theories of carcinogenesis are not mutually exclusive but complementary when considered within the two-phase model of carcinogenesis, which consists of *initiation* and *development*. Each phase may further consist of two or more steps. The initiation phase may require up to two, or at most a few genetic changes (gene mutations, chromosomal abnormalities), and this phase is probably irreversible. The developmental phase may involve two or more additional genetic and/or epigenetic changes. If the developmental phase involves epigenetic changes, it may be reversible. In this model, the sites of genetic or epigenetic changes are the tumor suppressor genes (*TS*-genes) that are specific for a given tissue or cell type. The oncogenes seem to be controlled by different sets of linked and/or unlinked *TS*-genes in specific tissues, accounting for differences in the incidence of human cancers. In the model, those *TS*-genes involved in the suppression of initiation are designated TS_I and others in development as TS_D. Changes in some putative TS_I genes may lead to initiation; impairment of TS_I gene function, among other things, may reduce the regulation of initiation of DNA synthesis. This initial mutation in TS_I may create a permissive environment for incipient cancer cells to undergo further mutations and genetic instability. On the other hand, impairment or changes in the state of TS_D genes may result in aberrant cell development. The expression of the malignant state may require the sequential and cumulative effects of genetic and epigenetic changes involved in carcinogenesis. In other words, the total *cancer experience is a multistep process*, presumably involving genetic changes in the TS_I genes for initiation, and impairment or change of state (epigenetic) of the TS_D genes for the development and malignant expression (Figure 1). Within this model, spontaneous or induced regression or reversal of tumor cells to the normal state may be centered on the developmental phase of carcinogenesis. The two-phase genetic concept of carcinogenesis is somewhat similar to the classical two-stage initiation and promotion model derived from mouse skin carcinogenesis. In the two-phase genetic concept, the genetic elements and the types of genetic changes occurring in each phase are clearly defined.

In its simplest form, the two-phase model for the origin of cancer may involve genetic changes in a pair of genes at a specific locus for initiation, followed by several additional genetic and/or epigenetic changes at other loci [53,54]. This situation may represent cancers in which predisposition is influenced by one or two genes, for example, retinoblastoma [55,56], xeroderma pigmentosum [57,58], and colon cancer [59]. However, in most human cancers, including those of the lung, stomach, breast, and prostate, initiation and development likely require alterations in more than two genes, with four to six mutations being a probable range. Although the precise mechanisms of cancer initiation remain speculative, it seems that both radiation and chemical carcinogens play an important role. The exact causes of cancer are not fully understood; however, certain environmental factors are considered likely contributors, such as tobacco smoke for lung cancer and dietary components, including animal fat, for stomach and colon cancers. The promoters may be directly or indirectly involved in the development of cancer. However, in the absence of initiation, promoters generally do not enhance the developmental phase of tumor formation. Several carcinogenic agents possess both initiating and promoting properties when administered at sufficient doses over time and are referred to as "complete carcinogens." Components of tobacco smoke fall into this category [60].

Thus, it appears that at least two classes of genes may be involved in the origin of cancer: *Tu* genes and proto-oncogenes. The current body of data indicates that proto-oncogenes are activated by dominant mutations (gain of function), whereas the recessive mutations resulting in the loss-of-function (inactivation) in the tumor suppressor genes, controlling *Tu* genes, seem to be involved in the inception of cancer [61]. The two-phase genetic model of cancer [53,54] is consistent with available data on a large number of human cancers involving specific chromosome aberrations, such as chronic myelogenous leukemia, Burkitt's lymphoma, and hereditary or sporadic cancers. Although the model presented in Figure 1 accounts for two genetic changes, namely recessive mutations in tumor suppressor genes resulting in loss of function, for the initiation of cancer, it can also accommodate a single dominant mutation with gain of function in a proto-oncogene for initiation, followed by a developmental phase in human cancers. The functional distinction between TS-I and TS-D genes in the two-phase model is based on theoretical classification. Single-cell sequencing of the TS-I and TS-D genes would be useful for verifying their function.

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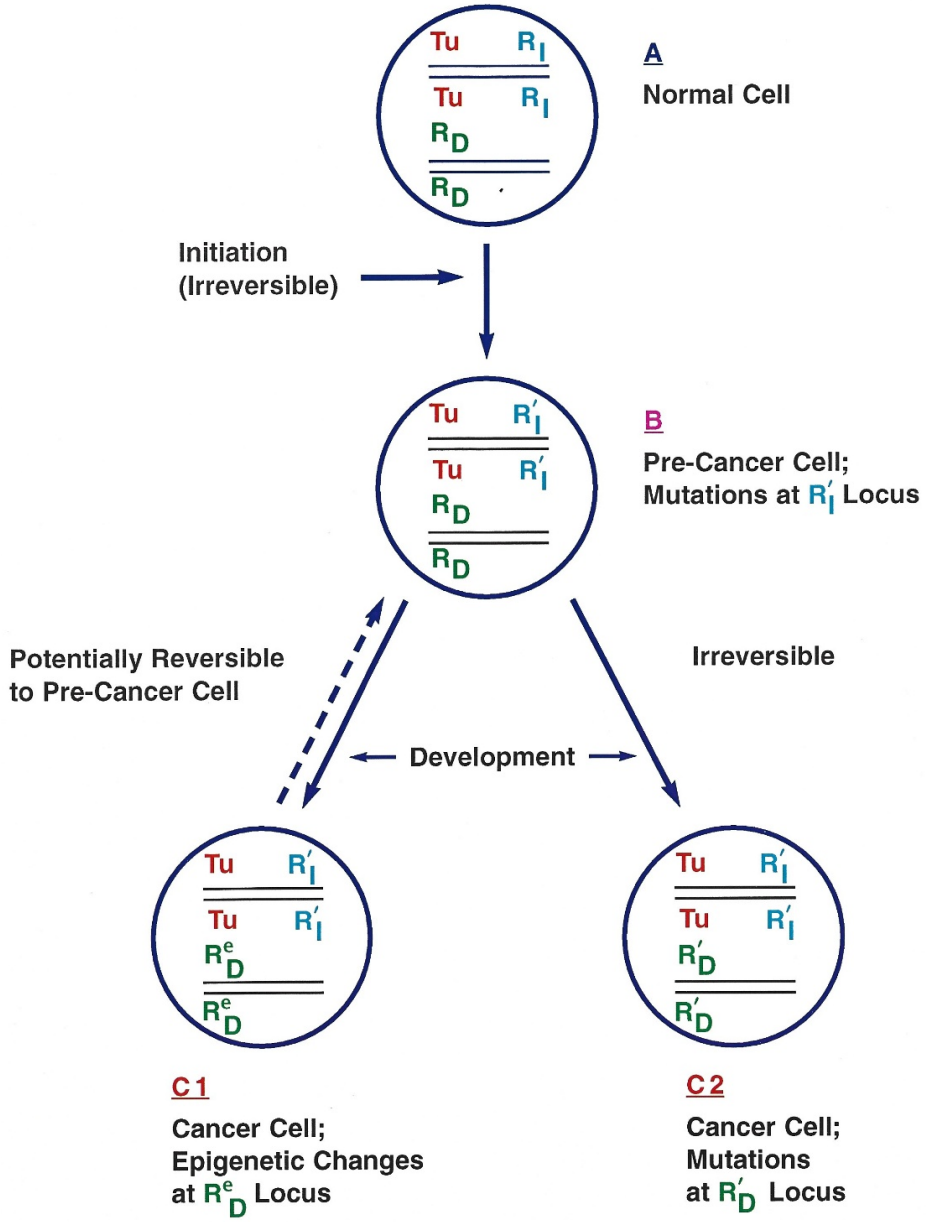

Figure 1: A simplified two-phase genetic-epigenetic model of carcinogenesis. Diagram showing a normal cell (A) with two pairs of chromosomes (other pairs of chromosomes in the complement are not shown), carrying the tumor suppressor genes (*TS*-genes), which suppress initiation (TS_I) and development (TS_D) of the tumor (*Tu*) gene in a neoplasm. Initiation of carcinogenesis (B) involves genetic changes (mutational events) in the TS_I elements (represented by *TS'I*), which are irreversible. The initiated pre-cancer cells may undergo differential growth, genetic or epigenetic changes, to give rise to cancer (malignant growth) in one of the two different pathways involving changes in the TS_D loci, and this mode of behavior may, in part, be intrinsically determined by the cell type. When TS_D genes undergo epigenetic changes (C 1; represented by $TS^e{}_D$), then the developmental phase is potentially reversible. On the other hand, when TS_D genes undergo mutational changes (C 2; represented by TS'_D), the developmental phase becomes irreversible.

6. Chromosomes, Genes, and Cancer

Following Boveri's postulate [36] that chromosome imbalance may be causally related to cancer, chromosome abnormalities have frequently been observed in the mitotic chromosomes of tumor cells. Early cytological observations using conventional staining techniques indicated that karyotypic variability occurs randomly during tumor progression [62–64]. However, specific types of chromosome abnormalities were subsequently discovered to occur frequently in certain human cancers, for example, chronic myelogenous leukemia [65] and meningioma [66, 67]. Recent karyotypic analyses using advanced staining

techniques have revealed that nonrandom chromosomal abnormalities may also be associated with several spontaneous human neoplasms, in addition to chronic myelogenous leukemia, meningioma, Burkitt's lymphoma, and other hematologic disorders [68,69]. It has also been possible to show that certain specific, and otherwise rare, types of chromosome abnormalities may occur frequently in chemically induced, as well as Rous Sarcoma Virus-induced animal tumors [70,71]. It would, therefore, appear that both in experimentally induced animal tumors and "spontaneous" human neoplasms, significant changes apparently involve specific chromosomes. Clearly, this indicates that certain genotypes carrying specific karyotypic abnormalities are more prone to neoplastic development than others.

Regarding the non-random nature of chromosomal abnormalities in certain spontaneous human cancers, it is relevant to ask: Are these chromosomal abnormalities the cause or the result of neoplastic development? Experimental evidence tends to support the notion that chronic myelogenous leukemia and Burkitt's lymphoma, as well as several human neoplasms, are clonal in origin and therefore might arise from rare genetic (mutational) changes [72–75]. Since specific chromosome aberrations (mutations) are present in primary tumors, it might be argued that these are somehow causally involved in the origin of cancer. The evidence suggests that specific chromosomal abnormalities are likely relevant to the initiation phase of certain spontaneous human neoplasms. Specific chromosomes involved in these neoplasms may carry genes necessary for the prevention of tumor formation, and aberrations or translocations of these genes, considered regulatory genes, may lead to the onset of tissue-specific neoplasms. The following neoplasms, involving specific chromosomal aberrations, are examined within the framework of the genetic concept of the origin of cancer. Although only two specific neoplasms are discussed below, other cancers involving specific chromosome aberrations may also be interpreted on the basis of the proposed model.

7. Chronic Myelogenous Leukemia (CML)

Approximately 90 percent of patients with CML carry the Philadelphia (Ph1) chromosome, which was assumed to be a loss of one half of the long arm of chromosome 22 [65,76]. Based on these observations, Ohno [77] suggested that a Ph1 chromosome-positive clone, which may eventually lead to CML, could arise from two mutational events: (1) loss of a leukemia-suppressing locus due to a deletion in the Ph1 chromosome, and (2) a somatic mutation of the homologous locus. Subsequently, however, it was shown by Rowley [76] that the chromosome fragment from the long arm of chromosome 22 was not really lost due to deletion, as was previously thought, but instead the fragment from chromosome 22 was translocated onto the long arm of chromosome 9 designated as t(9q+, 22q−), in most cases of the CML disease. Based on these observations, Comings [18] suggested that altered regulation of the leukemia-suppressing regulatory gene, due to a position effect from translocation from chromosome 22 to 9, accompanied by a mutational event in the homologous regulatory gene, presumably leads to Ph1 chromosome positivity in the Ph1 chromosome-positive leukemic clone. Approximately 10–15 percent of patients with CML lack the Ph1 chromosome [78,79]. These patients are generally older, and CML may have originated in them due to two somatic mutations in the regulatory loci on chromosome pair 22 [18].

It is known that the acute phase ("blast crisis") of CML, during which truly malignant transformation occurs, is associated with additional chromosomal changes superimposed on the Ph1 genotype in two-thirds of CML patients. The chromosomes involved in this variation are also non-random [74,76]. During the blast crisis, the four most common karyotypic changes include: (1) a second Ph^1 chromosome, that is, homozygosity for the Ph^1 chromosome, (2) trisomy for chromosome 8, (3) isochromosomy for the long arm of chromosome 17, and (4) an additional chromosome 19. Based on these overall observations across the chronic and acute phases, I propose that the development of CML may require more than two changes in a stepwise clonal evolution of the disease. Alterations present during the chronic phase may constitute the initiation process, arising from genetic changes in the $R_{I\text{-}CML}$ loci on chromosome 22. In contrast, changes associated with the blastic crisis may influence disease progression and malignant expression in chronic myelogenous leukemia and are presumed to involve alterations in the .$R_{D\text{-}CML}$ loci, likely located on chromosomes 8, 17, and 19. In one-third of patients with CML blast crisis, where the only consistently observed cytological abnormality is the Ph1 chromosome [76], the final changes in the RD-CML loci may arise from epigenetic and/or mutational events, without the involvement of specific gross chromosomal abnormalities

There are some observations that bear on the question of the hereditary versus acquired nature of CML. The presence of the Ph^1 chromosome only in the hemopoietic system, and the fact that if one of a pair of identical twins develops CML, the abnormal chromosome is only present in the affected twin, tends to support the notion that CML is a somatically conditioned neoplasm rather than an inborn error [80,81]. There are indications that clinically

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manifested leukemia may be preceded by a fairly long symptom-free period. Some cases are on record in which a portion of the bone marrow cells contains the Ph^1 chromosome years before the onset of the CML disease [82,83]. This observation is consistent with the idea that the presence of the Ph^1 chromosome may represent only the first step in the multi-step process underlying the development of CML.

Are any specific proto-oncogenes involved in the etiology of CML disease? Molecular studies have indicated that the specific chromosome translocation t(22q−, 9q+) brings together the *bcr* proto-oncogene from chromosomes 22 to the *abl* proto-oncogene on chromosome 9, thereby creating an inappropriate location for the *bcr* gene [68]. This position effect would presumably affect the transcriptional activities of the Ph^1 clones, so that excessive amounts of normal or aberrant proteins may be produced in the CML patients. The resulting fusion protein product has the amino terminus of the *bcr* protein joined to the carboxyl terminus of the ABL tyrosine kinase, so that the *abl* kinase domain becomes inappropriately active. However, the question arises: what regulates transcriptional control in Ph^1 cells? Proto-oncogenes do not regulate their own expression and therefore require control by regulatory genes.

8. Meningioma (MG)

Among all solid human neoplasms, meningiomas, which are benign brain tumors, are the most thoroughly investigated cytologically. The banding techniques have confirmed earlier observations, based on conventional staining procedures [66,67], that in tumor cells obtained from patients with MG, the primary change frequently involved a single chromosome 22 [66,67]. In most cases of MG, one chromosome 22 is missing; however, in some cases, the alteration involves the deletion of the distal part of chromosome 22(22q−). In contrast to the finding in chronic myelogenous leukemia (CML) with Ph^1, however, the deleted distal part of the chromosome does not appear to be translocated onto any other chromosome in the human complement [84,85]. Based on the available data on more than 200 cases of MG, Mark [86] has summarized the results of cytologic findings as follows: (1) the primary change affects one chromosome 22; either the entire chromosome 22 or part of it is lost; (2) superimposed on the primary change, additional changes take place, of which the most common involve losses of chromosomes 1, 8, and 9; and (3) about 60 percent of the MG cells show a chromosome stem line distribution in the hyperdiploid region, and only 33 percent are diploid; in the hyperdiploid region the 45 chromosome stem line outnumbered the others. Based on these observations on the benign MG tumors, it may be postulated that the following events, perhaps sequentially, are relevant to the origin of meningiomas: (1) a change from $TS_{I\text{-}22}$ to $TS^0{}_{I\text{-}22}$ by deletion of the chromosome 22 or its part thereof; (2) a change in the homologous $TS_{I\text{-}22}$ to $TS'_{I\text{-}22}$ due to a mutational event, and (3) one or more changes in the $R_{D\text{-}MG}$ loci specific for meningiomas probably take place, and such changes may result from monosomy of chromosomes 1, 8, and 9. These changes probably occur individually in separate cells, but perhaps not altogether in cells of the same tumor; therefore, the end result of these individual chromosomal abnormalities may be only the onset of benign brain tumors. The observation that the majority of tumor cells analyzed from MG fall within the diploid or hypodiploid range, with approximately 45 chromosomes, may lend support to the above hypothesis. On the other hand, the presence of aneuploidy does not always serve as a prerequisite for tumor development, nor does the absence of aneuploidy necessarily indicate the absence of tumors; gene mutations and developmental events can occur without apparent chromosomal abnormalities. However, the benign nature of these brain tumors leaves the questions about the developmental phase more or less open.

The consistent abnormality of chromosome 22 in such diverse neoplasms as meningiomas and chronic myelogenous leukemia raises some intriguing questions. Although it is conjectured that both of these neoplasms may be initiated by a certain primary genetic change in the chromosome 22, this primary genetic change may be caused in several different ways: (1) involvement of different etiologic agents; (2) involvement of different target sites on the chromosome 22 for the initiation of two neoplasms; and (3) the translocation 22 to 9 may represent a position effect highly specific for the initiation of the CML disease. Alternatively, loss of all or part of chromosome 22 may represent a common genetic initiating event in both MG and CML neoplasms; however, the resulting outcome may depend on the specific constellation of chromosomal aberrations in particular cell types and the subsequent differentiation events.

9. Genetic Nature of Hereditary Cancers

The genetic predisposition to hereditary cancers may depend on whether an individual carries one or two defective genes, which can be either dominant or recessive [83,87,88]. Although several human neoplasms, including retinoblastoma and polyposis of the colon, have been described as “dominantly inherited cancers”, it is not entirely clear whether cancer indeed behaves as a domi-

nant trait at the cellular level [15,83,89]. A dominantly inherited cancer refers to a condition in which a single altered allele significantly increases cancer risk. A gene for cancer would be correctly called dominant whether its effect was, invariably, to produce a cancer, or its effect would merely be to produce a greatly increased probability of cancer, when present in a single dose. The presence of a defective gene in retinoblastoma or colon polyposis apparently increases the probability of cancer [83,90], but a defective gene by itself does not lead to cancer. On the other hand, if a second mutation required to initiate cancer occurs at the homologous locus leading to the loss of heterozygosity (LOH), or acquisition of homozygosity, then this would imply that retinoblastoma and polyposis of the colon that behave as dominantly inherited cancers at the pedigree level, may behave as recessive disorders at the cellular level. Loss of heterozygosity (LOH) is considered an early event in multistep carcinogenesis. In the hereditary cancer category, the origin of the following neoplasms is examined based on a two-phase genetic model of cancer.

10. Retinoblastoma (RB)

Retinoblastoma is a malignant tumor of the eye that typically occurs in children between a few months and four years of age. About one child in 20,000 is afflicted with this cancer. There are two forms of retinoblastoma: one hereditary, which is transmitted as an autosomal dominant trait through the germline, and the second is a spontaneous, somatic-conditioned type [55,56,82,90]. In hereditary RB, one mutation is inherited through the germ cells, while the second mutation occurs in the somatic retinal cells, and multiple tumors develop in both eyes. On the other hand, in the spontaneous form of Rb, both mutations occur in the somatic retinal cells, and only one eye is affected by the tumor. The presence of a deletion in the long arm of chromosome 13 in several patients with hereditary, as well as sporadic RB [91,92] indicates that the specific deletion on chromosome 13 may carry genetic information involved in the genesis of Rb. These observations led Comings [18] to suggest that the two mutational events, either a deletion accompanied by a gene mutation or two gene mutations, occur in the regulatory loci, or tumor suppressor genes, likely located on chromosome 13. According to the biphasic genetic model of cancer origin, these two mutational events at the TSI-Rb locus may not necessarily produce a clinically recognizable tumor but may be instrumental in initiating a pre-tumor cell. Subsequently, additional genetic and/or epigenetic changes in the $TS_{D\text{-}Rb}$, another set of regulatory genes, must occur to produce a malignant tumor.

Using molecular analysis of the chromosome deletion associated with Rb, it was possible to clone and sequence the RB gene to better understand the genetic defect [93–95]. As would be expected on the basis of inherited genetic defects, the deletion or mutation of the *Rb* gene was found in every cell of the body. However, cells carrying only one mutation remain normal; the Rb clone is initiated only when the second copy of the RB gene is mutated in immature retinal cells. On the other hand, in the sporadic, non-hereditary form, there is no genetic defect in both RB gene alleles in normal cells; instead, both copies of the *RB* gene are mutated in the somatic (retinal) cells. Whatever the nature of the mutation, whether by deletion followed by a second deletion, or one deletion and one gene mutation, or both gene mutations in the *RB* locus, a loss of heterozygosity (LOH) in the *RB* gene has been observed in about 70 percent of the RB patients.

The RB gene is involved not only in the etiology of retinoblastoma but has also been found to be absent in several other unrelated neoplasms, including lung, breast, and bladder carcinomas [96]. The role of the *RB* gene in these neoplasms, although interesting, remains intriguing. Does the *RB* gene product play an important role in the regulation of the cell division cycle? It appears that *RB* protein alternates between a phosphorylated and an unphosphorylated state in the cell cycle, and it remains unphosphorylated in the cells that are not undergoing cell cycling [97]. In the later unphosphorylated state, the *RB* gene products bind to certain gene regulatory proteins and thereby prevent DNA replication and cell cycling. Loss of the *RB* regulatory gene product removes the restraint on cell division and cycling. Although the involvement of the *RB* gene in several different cancers, the developmental pathways in retinoblastoma and other neoplasms may be different, the latter probably requiring additional genetic and/or epigenetic changes at different loci for their cancerous growth.

11. Colorectal Cancer (CRC)

There is a strong hereditary predisposition to familial adenomatous polyposis coli (APC) in humans, and pedigree analyses suggest an autosomal dominant inheritance pattern [98]. APC is a non-malignant tumor that usually appears by the time an individual reaches adulthood. One serious aspect of this syndrome is that it invariably leads to malignant adenocarcinoma of the colon by age 50. The average age of death in the APC syndrome is 40 years [59]. It has been suggested [56] that APC might be initiated as a result of two mutational events, one of which is inherited via the germline, while the second mutation occurs in the somatic colonic cells. As with retinoblastoma, APC can also occur in the non-hereditary form. In the sporadic or

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non-hereditary form, the two mutational events would ostensibly occur in the somatic cells (epithelial lining) of the colon. However, two mutational events in the *APC* gene may only produce a benign tumor or polyp (adenoma), and for the malignant phenotype to arise, some additional genetic or epigenetic changes may be necessary. Here, then, the two events represented by the change from $TS_{I\text{-}APC}$ /$TS_{I\text{-}APC}$ to $TS^{'}_{I\text{-}APC}$ /$TS^{'}_{I\text{-}APC}$ may be instrumental in initiating the process that may result in a benign (polyposis) tumor. For malignant transformation to adenocarcinoma, additional genetic and/or epigenetic changes in another set of regulatory genes, designated RD-APC, located at one or more loci, may be required.

Molecular analysis has revealed that the tumor suppressor gene *APC*, associated with hereditary adenomatous polyposis coli (colon polyposis), is located on the long arm of chromosome 5. The disease can be attributed to deletion or inactivation of the *APC* gene [99]. In the hereditary form of APC, all the cells in the body carry the deletion or inactivating mutation on the *APC* gene; however, after the second mutation of the second copy of the APC gene, or LOH, the polyps appear only in the epithelial cells of the colon. On the other hand, in the non-hereditary form, the two mutations in the *APC* gene would occur in the somatic (epithelial) colonic cells, and the remaining cells in the body have normal copies of the *APC* gene. Since it takes more than a decade for benign adenoma to progress to malignant adenocarcinoma, it appears that several additional genetic/epigenetic changes are required for the development of this disease, consistent with the observation that APC mutations occur early in colorectal cancer [100]. Although the normal function of the *APC* protein is unknown, it has been found to bind β-catenin and may be involved in a control mechanism for site-specific cytoskeletal anchorage at cell junctions [101].

In addition to the impairment of the *APC* gene, loss of heterozygosity at some other tumor suppressor genes, for example, the p^{53} gene located on chromosome 17p, and the *DCC* (deleted in colon carcinoma) gene on chromosome 18q have been observed in more than 70 percent of the colon cancer [102,103].

The incidence of colorectal cancer (CRC) shows that there is considerable variation among racially or ethnically defined populations in multiracial countries. The incidence of CRC has changed over time. Depending on the genetic background, CRC exhibited varying prevalence in Argentina, Brazil, Colombia, Russia, and Thailand.

Besides mutations in the tumor suppressor genes, are there also mutations in the proto-oncogenes in human colorectal cancer? If so, how are they involved in the etiology of this cancer? It turns out that about 50 percent of the patients with APC have a point mutation in a *ras* proto-oncogene located on chromosome 12p (an activating mutation in codon 12 of the *K-ras* gene), and a few percent have amplified copies of the *myc* proto-oncogene [104]. However, the precise role of activated proto-oncogenes in their dominant state remains unclear in human cancer. Does the dominant mutation in a proto-oncogene activate it independently of the gene mutations leading to loss of heterozygosity (LOH) in the tumor suppressor genes, or do they somehow act synergistically for the origin of cancer? Summarizing the genetic events in colorectal cancer [103,105], it would appear that LOH of the tumor suppressor gene *APC* may be the primary initiating event, perhaps activating a proto-oncogene (*K-ras*) or another tumor gene, followed by mutations (LOH) at other suppressor genes (*DCC*, P^{53}) for the development and expression of the malignant state. Altogether, colorectal cancer may involve at least 7 mutations at four different gene loci, which is consistent with the present model.

12. Genetic Instability and Cancer

These observations on specific chromosome aberrations in several human cancers, as well as in cases of hereditary and non-hereditary tumors, are consistent with the idea that cancer is a multistep process. Although only four human cancers are discussed in this paper, it is predicted that other cancers, including lung, breast, and hemopoietic cancers, could also be interpreted using the two-phase genetic model of cancer. Although the concept of proto-oncogenes seems somewhat paradoxical in human cancer, the genetic changes in the other set of genes, the tumor suppressor genes, are probably more relevant to the genesis of human cancer, or at least the hereditary cancers. In any case, there must be incipient tumor genes or cancer genes in the human genome whose expression is controlled by tumor suppressor genes; these cancer genes are released from repression when tumor suppressor genes are inactivated by mutations.

It is evident that certain genotypes are more susceptible to neoplastic development than others. Cancer development appears to depend on interactions between the genetic material and the environment (both intrinsic and extrinsic). Although the mechanisms of transformation from a normal to a cancer cell are not yet fully understood, it is plausible that the diverse environmental factors, such as chemical carcinogens, ionizing radiation, and viruses, acting singly or in combination, may inactivate the tumor suppressor genes through mutational and/or epigenetic events, thereby resulting in the initiation and development of cancer. Initiation results from mutational events and is probably irreversible. While expression of a malignant state

may require additional genetic and/or epigenetic changes, if epigenetic, the developmental phase is potentially reversible. In this context, it should be mentioned that tumor regression, although rare, and reversals to the normal state have been recorded [46,47,49,106,107]. Although regression of tumors might be due to immunological mechanisms of the host, those cases of reversal to an apparently normal state need to be fully examined, since reversal may not always mean reversal to a completely "normal" condition. Revertant cells may still retain some properties of the progenitor tumor cell; thus, they may represent benign or "incipient tumor cells" corresponding to the initiation phase, and may be phenotypically and biochemically closer to normal cells than to fully developed tumor cells. In that case, reversal has most likely occurred in the developmental phase. Therefore, within the framework of the present genetic model, spontaneous or induced regression or reversal of tumors to a normal state may be centered on the developmental phase of carcinogenesis. The genetic and epigenetic changes in tumor formation may be sequential and cumulative.

The initial genetic alteration likely generates a heterogeneous population of cells from which new combinations advantageous for tumor expression and development may be selected [108–111]. Malignant tumors may arise from the loss of density-dependent growth regulation [112], or possibly through the interaction of fetal gene derepressors with the genome [113], leading to the production of mRNA for protein products involved in growth, invasiveness, and metastasis. The two-phase genetic model of carcinogenesis is compatible with observations from somatic hybridizations between malignant and normal cells in mice [114,115] and humans [116]. Subsequent inoculations into appropriate animal hosts suggest an apparent separation in the genetic control of transformed versus malignant phenotypes.

In its simplest form, the two-phase model of carcinogenesis may involve genetic changes in two genes at a particular locus for initiation, followed by a few genetic and/or epigenetic changes at other loci to give rise to cancerous cells. This kind of situation may be representative of most human cancers, whether hereditary or sporadic. Thus, it is predicted that both hereditary and non-hereditary cancers, including retinoblastoma and cancers of the lung, stomach, colon, prostate, and breast, likely require, in addition to two mutations for initiation, changes in several other genes, possibly four to six mutations, for full development.

Thus, it appears that at least two classes of genes may be involved in the origin of cancer: inherited tumor genes, or oncogenes, and tumor suppressor genes. The current body of data indicates that proto-oncogenes are activated by dominant mutations (gain-of-function), whereas the recessive mutations resulting in the loss-of-function (inactivation) in the tumor suppressor genes seem to be involved in the development of cancer [61]. However, the precise role of proto-oncogenes in human cancer remains an enigma. Alternatively, one or more oncogenes may be involved in the etiology of a specific type of cancer. Is it always necessary to have a dominant mutation to turn a proto-oncogene into an oncogene? Or mutations in certain proto-oncogenes may be deletional or recessive? Are the two gene mutations in the tumor suppressor genes adequate and sufficient to condition a normal cell into a pre-cancer cell? Would that remove the restraint on the expression of the tumor genes? Or do the proto-oncogenes must undergo genetic change for their expression? These are some of the intriguing questions in the genesis of cancer. However, the concept of oncogene in humans is somewhat puzzling and paradoxical. The standard assay for the identification of oncogenes does not test their effects on somatic human cells but on mouse-derived fibroblast cell lines, which have already undergone mutations at several loci, possibly including the tumor suppressor loci, so that they are easy to transform. It is possible that the tester mouse strains may not have stringent controls against the introduced oncogenes. In contrast, in long-lived humans, a more stringent set of tumor suppressor genes may have evolved to control and constrain cellular oncogenes, ensuring that, in most cases, the host remains unharmed. In spite of a large number of tumor suppressor genes, two, namely *Rb* and P^{53}, seem to be most frequently inactivated in more than 50 percent of human cancers. Both these genes are directly or indirectly involved in the control of cell division or tissue renewal through cyclin-dependent protein kinases [117], and it is possible that there may be sharing of some critical tumor suppressor genes in a number of cancers. However, the final outcome may depend on the developmental events specific to each cell type. The same may apply to oncogenes; that is, different oncogenes may be shared among various human cancers.

The current genetic model does not distinguish between hereditary and non-hereditary forms of cancer with respect to the genetic and epigenetic changes involved in disease initiation and progression. In the hereditary form, all cells in the body carry the defective gene, yet cancer typically develops in a specific, preprogrammed cell type or tissue, either during childhood or later in life. In contrast, in non-hereditary cancers, the target somatic tissue is not predisposed in the germline and becomes cancer-prone only after its tissue-specific tumor suppressor genes are impaired. Although most human cancers that occur in the hereditary form also occur in the non-hereditary form, these two forms may be discriminated by their time of

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development. It appears that in the hereditary form, predisposed individuals may develop cancer earlier than in the non-hereditary form, as they are born with a defective gene.

13. Conclusions

In conclusion, it may be stated with fatalistic resignation that, as long as there are living cells capable of division, there remains a possibility that they might become cancerous in multicellular organisms. Therefore, it is essential to identify, characterize potentially cancer-inducing genes, the tumor suppressor genes, their products, and genes that enhance tumor development, and induce aggressive and invasive malignant behavior. These studies would inform both cancer prevention strategies and therapeutic development. Therefore, understanding the genetic and molecular processes involved in normal cell division, differentiation, and behavior is critical to cancer research.

List of Abbreviations

APC	Adenomatous Polyposis Coli
CML	Chronic Myelogenous Leukemia
c-*onc*	Cellular Oncogenes
CRC	Colorectal Cancer
LOH	Loss of Heterozygosity
MG	Meningioma
Ph[1]	Philadelphia
RB	Retinoblastoma
R-genes	Regulatory Genes
RSV	Rous Sarcoma Virus
TS	Tumor Suppressor
Tu	Tumor Genes

Author Contributions

The author was responsible for all aspects of the manuscript, including conceptualization, literature search, data curation, visualization, writing—original draft, writing—review and editing, and final approval of the manuscript. The author completed and approved the final accepted version of the manuscript prior to his passing.

Conflicts of Interest

The author declares no conflicts of interest.

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AI Declaration

The author confirms that no AI tools were used to generate any content of this manuscript.

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