Genomed Connect
ISSN: 3105-3645
2025, Article ID. x, Cite as: https://www.doi.org/10.69709/xxx

SCIFINITI PUBLISHING

OPEN ACCESS

Review Article

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

Mulkh Raj Ahuja[†]

Independent researcher, 60 Shavertown Road, New Paltz, NY 12561, USA

E-mail: mrahuja@hotmail.com

[†]Mulkh Raj Ahuja, the sole author of this manuscript, passed away on 23 December 2025, after acceptance of the article on 26 November 2025. All scientific content and revisions were completed and approved by the author prior to his death. Following his passing, only minor editorial and formatting corrections were made at the proof stage. With written authorization from the next of kin, Ms Ila Ahuja is designated as the contact for post-publication correspondence.

Abstract

Cancer is a disease of living cells in the multicellular organisms. Its origins are closely associated with the evolution of multicellularity, which emerged billions of years ago. The “incipient cancer genes” (proto-oncogenes) presumably evolved from cell reproduction genes during the evolutionary transition from unicellular to multicellular organisms. Although initially these incipient cancer genes were involved in rapid cell division required for growth at specific developmental stages, their activity had to be regulated for a balanced growth and differentiation during evolution. Those genes that accomplish the necessary regulation and restraint of potentially cancer-inducing genes, so-called tumor genes (*Tu*) or cellular oncogenes (c-*onc*), are the tumor suppressor genes (*TS*). Cancer is a multistep process, involving a number of genes. In this review, human cancer is considered in the framework of a two-phase genetic model of carcinogenesis consisting of initiation and development.

In the two-phase model, the initiation phase may require up to two, or at the most a few genetic changes (gene mutations or chromosomal abnormalities); this phase is potentially irreversible. The developmental phase may involve two or more genetic and/or epigenetic changes. If it consists of epigenetic changes, the developmental phase is potentially reversible. In this model the sites of genetic or epigenetic changes are the *TS*-genes that are specific for a given tissue or cell type. The number of such regulatory tumor suppressor genes (*TS*-genes) may be different for different tissues. Diverse environmental factors, such as chemical carcinogens, ionizing radiation, and viruses, acting singly or in combination, may affect the function of the *TS*-genes either directly or indirectly through mutational or epigenetic effects, thereby resulting in initiation/development of cancer. This model accounts for hereditary as well as sporadic human cancers. Spontaneous or induced regression or reversal of tumor cells to normal state may be centred on the developmental phase of carcinogenesis. In this review, I propose that the origin of cancer genes is part of 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 cell in the multicellular organisms. And as long as there are living cells that are capable of division, there exists the possibility that they might become cancerous. *That seems to be the Tao of Cells*! The origin and evolution of the cancer cells goes back to the origin of life billions of years ago. In this review, I

propose that the origin of cancer genes is part of the evolutionary history of multicellular organisms. It is probable that life originated on the Planet Earth between 3 and 3.8 billion years ago [1]. The origin of the self-replicating molecule, whether autocatalytic protein polymer [2] or RNA or DNA was crucial to the development and evolution of life on Earth. The initial molecular systems could, in principle, both reproduce and evolve without having a Mendelian genome [2]. However, unicellular or multicellular systems require a genome for growth, differentiation, and evolution. In such systems DNA is the master molecule, which governs cellular structure, activities, and function. Although the genetic dictionary contains only four letters of the alphabet A (adenine), C (cytosine), G (guanine) and T (thymine), there is enormous potential, depending on the arrangement of the letters in the genetic code, for genetic variation and the origin of species. The first putative pre-life forms may have been relatively simple RNA or DNA viruses that could exist in the early hostile environment on Earth.

As life evolved from unicellular to multicellular forms, three-dimensional growth and differentiation were subsequently established as essential processes, in addition to cell reproduction, for further development and evolution of higher forms of life. I postulate that ancient “incipient cancer genes” (proto-oncogenes) that evolved in the retroviruses later became incorporated multicellular organisms during the evolutionary process [3]. Although initially these proto-oncogenes genes were involved in rapid cell division required for growth at specific developmental stages, their activity had to be regulated for balanced growth and differentiation. For the regulation of the proto-oncogenes another set of gene evolved, the so-called tumor suppressor genes that controlled the activity of the proto-oncogenes Thus, two types

of cancer-related genes (tumor suppressor genes and proto-oncogenes) co-exist in the multicellular genome, including humans.

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

2. Cancer Origin and Regulation

The adult human male body, on the average, consists of some 36 trillion cells, while the adult female body consists of 28 trillion cells [9]. There are over 400 cell types, including 145 types of neurons, in the human body [9, 10]. Although the precise number of cancer genes in humans remains an open question at the present time. 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 of different tissues/organs, it may be postulated that the cancer genes in different organs are controlled/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 antioncogenes (*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 and/or unlinked to the oncogenes. Elimination of *R*-genes or impairment of *R*-gene function by radiation, or chemical carcinogenesis, or viruses, would release the oncogene from the restraint and trigger a chain of events which may lead to the development of tissue-specific neoplasms [13-14]. Cancer initiation and development occurs in multiple stages. Following initiation phase, the initial cell undergoes primary changes that makes it neoplastic. Subsequent changes by mutations would promote clonal selection, leading to neoplastic development. In other words, carcinogenesis involves tumor initiation and clonal evolution of tumor cells [22, 23]. For clarity, we shall denote cancer gene or oncogene as *Tu* (tumor gene) and their regulatory gene *TS* (tumor suppressor gene) for the remaining of the text.

For the purposes of discussion in this paper, we shall mainly focus on the *Tu* genes in hereditary and no-hereditary cancers. The precise function of these genes remains conjectural. However, it seems probable that these potentially cancer-causing genes are transiently active during different stages of embryonic development or 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 for 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 the cancer genes from the normal constraint and may lead to the development of neoplasms [13,14].

Tumor suppressor genes play a crucial role in the development of a large array of human cancers. They can be affected by environmental factors. The molecular mechanisms behind variation in the tumor suppressor genes may involve genetic changes at different locations in the genome depending upon the tissue/organ type. Future research in molecular genetics may provide more insight into these questions.

Proto-oncogene activation and tumor suppressor gene inactivation synergistically promote cancer and form a target group in cells of neoplasms. I speculate that proto-oncogene might be first activated to the state before tumor suppressor genes are inactivated. But we need more evidence to support this hypothesis.

3. Genetic Change and Cancer

It has been variously estimated that more than 75 percent of human cancers are due to environmental factors, for example, cigarette smoke, asbestos, chemical carcinogens, ultraviolet rays, and X-rays [25-28]. Viruses have also been implicated in the etiology of some human cancers [29-31]. Although the precise mechanisms of transformation of a normal cell to a cancer cell are not yet fully understood, it seems probable that these diverse environmental factors, singly or in combination, may affect the genetic components of the cell. They may impair the tumor suppressor (*TS*) genes by causing a certain genetic change (gene mutation or chromosomal aberration, or genetic transposition) [32, 33], or by inducing an epigenetic (developmental) change [34, 35].

The mutation concept of cancer goes back to the beginning of the present century, when Theodore Boveri published a classic book entitled “Zur Frage der Entstehung maligner Tumoren” (On the Origin of Malignant Tumors) in 1914 [36]. Based on his keen observations in cell biology, Boveri concluded that: (1) tumor cells are derived from normal cells, and causes of abnormalities are inherent in the tumor cells, and (2) cells of malignant tumors have a cellular defect, having lost part of the normal cellular component(s). Boveri further postulated that the abnormal morphology of chromosomes (in particular chromatin complex) frequently observed in tumor cells were central to the origin of tumors. Boveri’s concept of the abnormal chromatic 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 manner by which mutations produce malignancy is still enigmatic. Carcinogens interact with DNA and cause damage to it. If this damage is not repaired properly, it is fixed as a mutation in the replicating DNA molecule. Mutations affecting the genes involved directly or indirectly in the regulation of cell reproduction and differentiation may lead to onset of neoplastic development.

Environmental factors affect the function of tumor suppressor genes. However, it appears that environmental factors induce methylation in tumor suppressor genes. Cigarette smoke carcinogens, and other harmful environmental factors cause extensive DNA damage, genomic alterations

4. Epigenetics in Cancer Development

The word epigenetics was introduced by the British embryologist Conrad Waddington in 1942 and defined epigenetics 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 behind variation in the tumor suppressor genes may involve genetic changes at different locations in the genome depending upon the tissue/organ type. Future research in molecular genetics may provide more insight into these questions.

Epigenetics involves changes in the genes by silencing and modifying gene expression, but not by changing the structure of the genes by 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 underlying implication of the developmental or differentiation theory is that cancer need not be mutational in origin, but it could result from epigenetic changes [38-42]. Epigenetic transcriptional mechanisms along with unlocking the phenotypic plasticity during tumor evolution plays an important role in cancer development [43, 44]. The prevalent view is that development and differentiation are the result of epigenetically controlled changes in the expression of various genes and not the result of changes in the structure of genetic material. Similarly, cancer, which is characterized by a defect in differentiation, may be the result of an epigenetic change [45] in the expression of gene(s) and not due to a change (mutation) 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 invoke the presence of specific cancer genes. But instead considers that certain tissue-specific epigenetic genes generally involved in cell reproduction and tissue differentiation, when misprogrammed may lead to neoplastic development [50]. However, more recently it also considers cancer promoting genes (or cellular oncogenes) as the potential targets of epigenetics [51, 52]. Regardless of the cancer epigenetics

hypothesis, there exists the probability that there will be interaction between mutational and developmental events in cancer development.

Epigenetic mechanisms are essential for normal development and tissue specific gene expression patterns. The primary changes in epigenetic gene silencing are: (1) DNA methylation.

5. A Genetic/Epigenetic Concept of Cancer

I suggest that genetic and epigenetic theories of carcinogenesis are not mutually exclusive, but complementary if we consider tumor formation in the framework of two-phase model of carcinogenesis consisting of *initiation* and *development*. Each phase may further consist of two or more steps. The initiation phase may require up to two, or at the most a few genetic changes (gene mutations, chromosomal abnormalities), and this phase is probably irreversible. The developmental phase may involve additional two or more genetic and/or epigenetic changes. If the developmental phase consists of epigenetic changes, then it is potentially 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, to account for the differences in the incidence of different 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 of the putative TS_I genes may result in initiation; impairment of TS_I gene function, among other things, may result in decreased regulation of initiation of DNA synthesis. This initial mutation in the TS_I may provide milieu for the incipient cancer cells for further mutations and genetic instability. On the other hand, impairment or change of state of the TS_D genes may

result in aberrant cell development. The expression of the malignant state may require a sequential and cumulative effect of genetic and epigenetic changes involved in the initiation and development of 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). In the framework of this model, spontaneous or induced regression or reversal of tumor cells to the normal state may be centred 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 the mouse skin carcinogenesis system. However, in the two-phase genetic concept, the genetic elements and the kind of genetic changes in each phase are outlined.

In the simplest form, the two-phase model for the origin of cancer may involve genetic changes in a pair of genes at a particular locus for initiation, followed by a few to several genetic and/or epigenetic changes at other loci [53, 54]. This kind of situation may be representative of human cancers whose predisposition is controlled in inheritance by one or two genes, for example, retinoblastoma [55, 56] and xeroderma pigmentosum [57, 58], and colon cancer [59]. However, in most human cancers, involving the lung, stomach, breast, prostate probably require changes at more than two genes (very likely four to six mutations) for the initiation and development of these cancers. Although the precise mechanisms of initiation of human cancer are still speculative, it seems that both radiation and chemical carcinogens play an important role. It is also not clear what causes the development of cancer, but certain environmental factors appear to be good candidates, for example, tobacco smoke for lung cancer, and ingredients of diet (animal fat) for stomach and

colon cancer. The promoters may be directly or indirectly involved in the development of cancer. However, in the absence of initiation, the promoters will not generally enhance the developmental phase of tumor formation. A number of carcinogenic agents have both initiating and promoting properties if given in sufficient doses over a period of time, and are called 'complete carcinogens'. Ingredients of tobacco smoke belong to this category [60].

Thus, it would appear that at least two classes of genes may be involved in the origin of cancer: the *Tu* genes and the proto-oncogenes The current body of data indicate that 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, seems to be involved in the inception of cancer [61]. The two-phase genetic model of cancer [53, 54] is compatible with the available data in a large number of human cancers involving specific chromosome aberrations, for example, chronic myelogenous leukemia, Burkitt's lymphoma, and hereditary or sporadic cancers. Although, the model presented in Figure 1 accounts for two genetic changes (recessive mutations in tumor suppressor genes; loss of function) for initiation of cancer, the same model could account for a single dominant mutation (gain-of-function) in the proto-oncogene for initiation, followed by a development 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 in TS-I and TS-D genes would be useful in verifying their function.

6. Chromosomes, Genes, and Cancer

Following the postulate of Boveri [36] that chromosome imbalance may be causally related to cancer, chromosome abnormalities have been frequently observed in the

mitotic chromosomes of the tumor cells. Early cytological observations, based on conventional staining techniques, indicated that karyotypic variability was a random event occurring during the progression of tumors [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 based on newer staining procedures have revealed that non-random chromosome abnormalities may also be associated with several spontaneous human neoplasms other than chronic myelogenous leukemia and 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 would indicate 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 chromosomes 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 originate as a result of 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. I tend to favor the notion that specific chromosome abnormalities are relevant to the initiation phase of

certain spontaneous human neoplasms associated with them. Specific chromosomes involved in these neoplasms may carry certain genes necessary for the prevention of tumor formation, and aberrations/translocation of these genes, which I consider regulatory genes, may lead to the onset of tissue-specific neoplasms. The following neoplasms, involving specific chromosome aberrations, are examined on the basis 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 on the proposed model.

7. Chronic Myelogenous Leukemia (CML)

About 90 percent of the patients with the CML disease have a Philadelphia (Ph^1) 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 Ph^1 chromosome positive clone, which may eventually lead to the CML disease, may arise due to two mutational events: (1) a loss of leukemia-suppressing locus due to deletion in the Ph^1 chromosome, accompanied by, (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 position effect by translocation from chromosome 22 to 9, accompanied by a mutational event in the homologous regulatory gene, presumably leads to Ph^1 chromosome positive leukemic clone. About 10-15 percent of the CML patients do not have the Ph^1

chromosome [78, 79]. These are somewhat older patients, and the CML disease may have originated in them due to two somatic mutations in the regulatory loci on the chromosome pair 22 [18].

It is known that the acute phase ("blast crisis") of the CML disease, during which truly malignant transformation takes place, is associated with additional chromosomal changes superimposed on the Ph^1 genotype in two-thirds of the 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. On the basis of these overall observations on the chronic and acute phases, I propose that the development of CML may require more than two changes in a step-wise clonal evolution of the disease. Of those present in the chronic phase may constitute the initiation process, resulting from genetic changes in the $R_{I\text{-}CML}$ loci on chromosome 22, while those changes in the blastic crisis may influence the course of development and malignant expression of the CML disease and presumably involve changes in the $R_{D\text{-}CML}$ loci, presumably located on chromosomes 8, 17 and 19. In one-third of the patients in the blast crisis of CML where the only consistently observed cytological abnormality is the Ph^1 chromosome [76], the last few changes in the $R_{D\text{-}CML}$ loci may arise due to epigenetic and/or mutational events without the involvement of specific, gross chromosome abnormalities.

There are some observations that bear on the question regarding the hereditary vs. acquired nature of the CML disease. 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, tend to support the notion that CML is a somatic-conditioned neoplasm rather that an inborn error [80, 81]. There are indications that clinically 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 contain 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 Ph^1 chromosome may only represent a first step in the multi-step process involved in the development of the CML disease.

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 *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 with to the carboxyl terminus of the *abl* tyrosine protein kinase, so that *abl* kinase domain becomes inappropriately active. However, the question arises, what regulates the transcriptional control in the Ph^1 cells? The proto-oncogenes can themselves not control their own expression; they must be controlled by the regulatory genes.

8. Meningioma (MG)

Of all the solid human neoplasms, the meningiomas (benign tumors of the brain) are cytologically the most thoroughly investigated tumor type. The banding techniques have confirmed earlier observations, based on conventional staining procedures [66,

67], that in the tumor cells obtained from patients with MG the primary change frequently involved one chromosome 22 [66, 67]. In most cases with MG, one chromosome 22 is missing; however, in some the affected change involved the deletion of the distal part of the 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 on 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 the cells of the same tumor, and therefore, the end result of these individual chromosomal abnormalities may only lead to the onset of benign tumors of the brain. The observation that majority of tumor cells analysed from MG are in the diploid or hypodiploid range (45 chromosomes) range may lend support to the above hypothesis. On the other hand, the presence of

aneuploidy does not always serve as a prerequisite for the development of tumors, or conversely the absence of aneuploidy may not serve as a criterion for the lack of tumors; gene mutations and developmental events normally do occur without the involvement of any apparent chromosomal abnormality. However, the benign nature of these brain tumors leaves the questions about the developmental phase more or less open.

The consistent abnormality of the chromosome 22 in such diverse neoplasms as meningiomas and chronic myelogenous leukemia raise 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 entire or part of chromosome 22 may be a genetic initiating event common to both MG and CML neoplasms, but that the nature of the result may depend on the precise constellation of the chromosome aberration in specific cell types and the differentiation events that follow.

9. Genetic Nature of Hereditary Cancers

The genetic predisposition to develop hereditary cancers may depend on the individual's possession of one or two defective genes, which may be dominant or recessive [87, 83, 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 dominant trait at the cellular

level [15, 83, 89]. A dominantly inherited cancer would be one whose appearance depends on a gene that has about the same degree of effect in single as in double dosage. 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 the case of retinoblastoma or polyposis of the colon apparently increases the probability that cancer would occur [83, 90], but the dominant gene by itself does not lead to the development of 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. The LOH seems to be a first step in the multistep development of cancer. In the hereditary cancer category, the origin of the following neoplasms is examined based on two-phase genetic model of cancer.

10. Retinoblastoma (RB)

Retinoblastoma is a malignant eye tumor that usually occurs in children from a few months to 4 years of age. About one child in 20,000 is inflicted 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 the hereditary RB, one mutation is inherited via the germinal cells, while the second mutation occurs in the somatic retinal cells, and multiple tumors occur 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] indicate 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, whether by a deletion accompanied by gene mutation, or both gene mutations, occur in the regulatory loci or tumor suppressor genes probably located on chromosome 13. According to the biphasic genetic concept of the origin of cancer, these two mutational events in the $TS_{I\text{-}Rb}$ 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 in to produce a malignant tumor.

By employing molecular analysis of the chromosome deletion associated with Rb, it was possible to clone and sequence the *RB* gene for a better understanding of 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, those cells carrying only one mutation remain normal; Rb clone is initiated only when the second copy of the *RB* gene has mutated in the immature retinal cells. On the other hand, in the sporadic, non-hereditary form, there is no genetic defect in both alleles of the *RB* gene in the normal cells, but 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 not only involved in the etiology of retinoblastoma, but it has been found to missing in several other unrelated neoplasms, for example, carcinomas

of the lung, breast, and bladder cancer [96]. The role of the *RB* gene in these neoplasms, although interesting, remains intriguing. Does *RB* gene product play an important role in the regulation of 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 prevents DNA replication and cell cycling. Loss of the *RB* regulatory gene product removes the restraint on cell division and cycling. Albeit 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 for the familial adenomatous polyposis coli (APC) in humans, and pedigree analyses suggest an autosomal dominant mode of inheritance [98]. APC is a non-malignant tumor which usually appears by the time an individual reaches adulthood. One of the serious aspects of this syndrome is that invariably it leads to malignant adenocarcinoma of the colon by the 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 in the case of retinoblastoma, APC also occurs in the non-hereditary form. In the sporadic or 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 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, some additional genetic and/or epigenetic changes in another set of regulatory genes designated $R_{D\text{-}ACP}$ located at one or more loci may be required.

Molecular analysis has revealed that the tumor suppressor gene *APC* (for hereditary adenomatous polyposis coli or polyposis of the colon) may be located on the long arm of chromosome 5; the disease can be traced 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 remaining cells in the body have normal copies of the *APC* gene. Since it takes more than a decade to progress from benign adenoma to malignant adenocarcinoma, it appears that several additional genetic/epigenetic changes would be required for the development of this disease, an idea consistent with the observation that *APC* mutations occur early during colorectal cancer [100]. Although the normal function of *APC* protein is not known, it has been found to bind to β-catenin and may be involved in some control mechanism in site-specific anchorage of the cytoskeleton at the cell junctions [101].

In addition to the impairment of *APC* gene, loss of heterozygosity at some other tumor suppressor genes, for example P^{53} gene located on chromosome 17p, and

DDC (deleted in colon carcinoma) gene on chromosome 18q have been observed in more than 70 percent of the colonic 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 upon the genetic background CRC exhibited varying prevalence in Argentina, Brazil, Columbia, Russia, and Thailand.

Besides mutations in the tumor suppressor genes, are there also mutations in the proto-oncogenes in the 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 an amplified copies of the *myc* proto-oncogene [104]. However, the precise role of activated proto-oncogenes to 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 are they somehow act synergistically for the origin of cancer? Summarizing the genetic events in the colorectal cancer [103, 105], it would appear that LOH of the tumor suppressor gene *APC* may be 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, the 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 the specific chromosome aberrations in several human cancers, as well as on those cases of hereditary and non-hereditary tumors are compatible with the idea that cancer is a multistep process. Although only four different human cancers are discussed in this paper, it is predicted that other cancers, including those of lung, breast, and hemopoietic cells could also be interpreted on the basis of 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 the tumor suppressor genes; the cancer genes are released from the restraint of repression following inactivating mutations of tumor suppressor genes.

It is apparent that certain genotypes are more prone to neoplastic development than others. The development of cancer seems to be dependent upon an interaction 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 initiation and development of cancer. Initiation results from mutational events, and is probably irreversible. While expression to 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 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 apparently normal state need to be fully examined, since reversal may not always mean reversal to completely “normal” condition. The revertant cells may still retain some of the properties of the progenitor tumor cell; thus they could represent benign or “incipient tumor cells” (initiation phase), which may be phenotypically and biochemically more close to normal cells than tumor cells. In that case, reversal has most likely occurred in the developmental phase. Therefore, in the framework of present genetic model, spontaneous or induced regression or reversal of tumors to normal state may be centred on the developmental phase of carcinogenesis. The genetic and epigenetic changes in tumor formation may be sequential and cumulative.

The initial genetic change probably results in a highly variable population of cells from which new combinations with advantageous to the expression and development of tumors may be selected [108, 109, 110, 111]. The malignant tumor may result from loss of density-dependent regulation of growth [112], or perhaps by interaction of fetal gene derepressors with the genome [113] to produce mRNA for the protein products involved in growth, invasiveness, and metastasis. The two-phase genetic model of carcinogenesis is compatible with the view, which is based on observations on somatic hybridizations between malignant and normal cells in mouse [114, 115] and humans [116] and their subsequent inoculations in appropriate animal hosts, that there is a apparent separation in the genetic control of transformed versus malignant phenotype.

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 hereditary as well as non-hereditary cancers including retinoblastoma and those of lung, stomach, colon, prostate, and breast probably require, in addition to two mutations for initiation, changes at several genes (four to six mutations) for the development of these cancers.

Thus, it would appear that at least two classes of genes may be involved in the origin of cancer: the inherited tumor genes or oncogenes and the tumor suppressor genes. The current body of data indicate 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 seems be involved in the development of cancer [61]. However, the precise role of proto-oncogenes in the human cancer remains an enigma. Or for that matter if one or more oncogenes are involved in the etiology of one 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 mutation 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 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 fibroblasts 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 a stringent control against the introduced oncogenes. On the other hand, in the long-lived humans a more stringent set of tumor suppressor genes may have evolved for the control and

constraint of cellular oncogenes, so that in most instances the host remains unharmed. In spite of a large number of tumor suppressor genes, two, namely *Rb* and P^{53} seem to most frequently inactivated in more than 50 percent of the human cancer. 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. But the final outcome may depend on the developmental events in each cell type. The same may be true of the oncogenes, that is, there may some sharing of different oncogenes in human cancers.

The present genetic model does not discriminate between hereditary and non-hereditary forms of cancer in terms of the genetic and epigenetic changes involved in the initiation and development of the disease. In the hereditary form all the cells in the body contain the defective gene, but cancer generally develops in a pre-programmed specific cell type/tissue either in childhood or late in life. On the other hand, in the non-hereditary cancers, the target somatic tissue is not conditioned in the germline, but 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 development. It appears that in the hereditarily form the predisposed individuals may develop cancer earlier than in its counterpart non-hereditary form, because the predisposed individuals are born with a defective gene.

13. Concluding Statement

In conclusion, it may be stated with fatalistic resignation that as long as there are living cells capable of cell division, there remains a possibility that they might become cancerous in the multicellular organisms. Therefore, it is essential to identify,

characterize potentially cancer-inducing genes, the tumor suppressor genes, their products, and gene that enhance tumor development, and induce aggressive and invasive malignant behavior. These studies would not only be valuable for identification of environmental carcinogenesis involved in the induction of human cancer and strategies to prevent them,

but also offer prospects for cancer therapies. Therefore, an understanding of the biological processes at the genetic and molecular levels involved in normal cell division, differentiation, and behavior would be critical for cancer research.

List of abbreviations:

Tumor genes (*Tu*)

cellular oncogenes (c-*onc*)

Tumor suppressor (*TS*)

Rous Sarcoma Virus (RSV)

Regulatory genes (*R*-genes)

Chronic Myelogenous Leukemia (CML)

Philadelphia (Ph^1)

Meningioma (MG)

Loss of Heterozygosity (LOH)

Retinoblastoma (RB)

Adenomatous Polyposis Coli (APC)

Colorectal Cancer (CRC)

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.

Conflicts of Interest

The author declares no conflicts of interest.

Funding

This work received no external funding.

Acknowledgment:

The author confirms that all content of the manuscript (including figures), was developed without the use of artificial intelligence or AI-assisted technologies.

References

1. Holland, H.D. Evidence for life on earth more than 3850 million years ago. Science. 1997, 275:38-39.
2. Kauffman, S.A. The Origins of Order. 1993, Oxford University Press, New York.
3. Ahuja, M.R. Cancer Causes and Prevention. 1997, UBS Publishers' Distributors, New Delhi/London.
4. Rous, P. a transmissible avian neoplasm (Sarcoma of the common fowl). J. Exptl. Med. 1910, 12:696-70.
5. Sajjad, H., Imtiaz, S., Noor, T, Siddiqui, Y.H, Sajjad, A, Zia, M. Cancer models in preclinical research: A chronicle review of advancement in effective cancer research. 2021, Anim Models Exp. Med. 4:87-103.
6. Das D, Banerjee A, Pathak, S, Paul. Importance of animal models in the field of cancer research. In: Pathak, S et al. Handbook of Animal Models and its use in Cancer Research. Springer Nature Singapore. 2023, pp. 1-25.
7. Anders, F, Schartl, M, Barnekow, A, and Anders, A. Xiphophorus as an in vivo model for studies on normal and defective control of oncogenes. 1984, Advances Advancer Research 42:191-273.

8. Schartl, M. and Lu, Y. Validity of Xiphophorus fish as models for human disease. Disease Models & Mechanisms. 2024, 17(1). Doi: https://doi.org/10.1242/dmm.050382
9. Hutton, I.A., Galbraith, E.D., Merleau N.S.C., Miettinen T.P., Smith, B.M., and Shander J.A. (2023) The human cell counts and size distribution. Proc. Natl. Acad. Sci. USA 120:1-10. https://doi.org/10.1073/pnas.2303077120
10. Vikaryous, M.K. and Hall, B.K. (2006) Human cell type diversity, evolution, development, and classification with special reference to cell developed from neural crest. Biol. Rev. 1-31. https://doi.org/10.1017/S1464793106007068Digital Object Identifier (DOI)
11. Chial, H. (2008) Proto-oncogenes to oncogenes to cancer. Nature Education 1:33.
12. Sinkala, M. (2023) Mutational landscape of cancer-driven genes across human cancers. Scientific Reports 13:12742.
13. Ahuja M.R., and Anders, F. A genetic concept of the origin of cancer, based in part upon studies in neoplasms in fishes. In: Prog. Exptl. Tumor Research. 1976, 20:380-397.
14. Ahuja, M.R, and Anders, F. Cancer as a problem of gene regulation. In: Gallo, R.C. Recent Advances in Cancer Research: Cell Biology, Molecular Biology, and Tumor Virology. Volume 1. 1977, pp. 103-117.
15. Knudson, A.G. (1985) Hereditary cancer, oncogenes and antioncogenes. Cancer Res. 45:1437-1443.
16. Lipsick, J. (2020) A history of cancer research: tumor suppressor genes. Coldspring Harb. Perspect. Biol. Doi:1101/chperspect.10.1101.

17. Dukal, T.C., Dhabhai, B., Pant, A., Moar, K, Chaudhary, K., Yadav, V., et al. (2024) Oncogenes and tumor suppressor genes: function and roles. MedCom. 5:e582

18. Comings, D.E. (1973) A general theory of carcinogenesis. Proc. Natl. Acad. Sci. USA 70:3324-3328.

19. Bishop, J.M. (1982) Oncogenes. Sci. Am. 246(3):80-92.

20. Varmus, H.E. (1984) The molecular genetics of cellular oncogenes. Ann. Rev. Genet. 18:553-612.

21. Klein, G. (1993) Oncogenes. In: Cancer Medicine, Third Edition. JF Holland, E Frei, RC Bast, DW Kufe, DL Morton, RR Weichselbaum (Eds). Lea & Febiger, Philadelphia, pp. 65-77.

22. Nowell, P.C, The clonal evolution of tumor cell populations. 1976, Science 194:23-28.

23. Greaves, M, and Maley, C.C. Clonal evolution in cancer. 2012, Nature 481:306-313.

24. Vogelstein, B, Kinzler, K.W. Cancer genes and the pathway they control. 2004, Nature Medicine 10:789-799.

25. Doll, R. (1977) Strategy for detection of cancer hazard to man. Nature 265:589-596.

26. Doll, R., and Peto, R. (1981) The Causes of Cancer. Oxford University Press, New York.

27. Epstein, S.S. (1974) Environmental determinants of human cancer. Cancer Res. 34:2425-2435.

28. Perera, F.P. (1997) Environment and cancer: Who are susceptible? Science 278:1068-1073.

29. Huebner, R.J. and Todaro, D.J. Oncogenes of RNA tumor viruses as determinants of cancer. 1969, Proc. Natl. Acad. Sci. USA. 64:1087-1094.

30. Zur Hausen, H. (1991) Viruses in human cancer. Science 254:1167-1173.

31. Wyke, J.A. (1991) Viruses and cancer. In: Introduction to the Cellular and Molecular Biology of Cancer, 2nd Edition. Franks, L.M., and Teich, N.M. (Eds). Oxford University Press, London, pp. 203-229.

32. Kainov, Y, Hamid, F, Makeyev, E. Recurrent disruption of tumor suppressor genes in cancer by somatic mutations in cleavage and polyadenylation signals. 2024, eLife 13:PR99040.

33. Chen, L, Liu, S, and Tao, Y. Regulating tumor suppressor genes: post-transcriptional modification. 2020, signal Transduction and Targeted Therapy 5:90.

34. IIango, S, Paital, B, Jayachandaran, P, Padma, P, R, Nirmaladevi, R. Epigenetic alterations in cancer. 2020, Frontiers in Biosciences, Landmark, 25:1058-1109.

35. Kazanets, A, Shorstova, T, Himli, K, Marques, M, Witcher, M. Epigenetic silencing of tumor suppressor genes: paradigms, puzzles, and potential. 2016, Biochimica et Biophysica Acta 1865:275-288.

36. Boveri, T. Zur Frage der Entstehung maligner Tumoren. 1914, Gustav Fischer, Jena.

37. Waddington, C.H. Canalization of development and the inheritance of acquired characters. 1942, Nature 150:563-565.

38. Pathak, A, Tomar, S, Pathak, S. Epigenetics and cancer: A comprehensive Review. 2023, Asian Pac. J. Cancer Biol. 8:75-89.

39. Baylin, S.B, and Jones, P.J. Epigenetic determinants of cancer. 2016, Coldspring Harb. Perspect. Biol. 8:a01 9505.

40. Esteller, M, Dawson, M.A, Kadoch, C, Rassool, F, Jones, P.J, and Baylin, S.B. The epigenetic hallmarks of cancer. 2024, Cancer Discovery October 2024: 1783-1809.
41. Capp, j-p, Aliga B, Pancaldi, V. Evidence of epigenetic oncogenesis: A turning point in cancer research. 2025, Bioassays. 47:e202400183.
42. Martinez, A-M, and Cavalli, G. A possible role of epigenetics in cancer initiation. 2025, Comptes Rendu Biologies 348:43-53.
43. Hanahan, D. Hallmarks of cancer: New dimensions. 2022, Cancer Discover 12:31-46.
44. Davies, A, Zoubeidi, A, Betran, H, Seth, L,A. transcriptional and epigenetic landscape of cancer cell lineage plasticity. 2023, Cancer Discovery 13:1771-1788.
45. Markert, C.L. (1968) Neoplasia: a disease of cell differentiation. Cancer Res. 28:1908-1914.
46. Braun, A.C. (1981) An epigenetic model for the origin of cancer. Quart. Rev. Biol. 56:33-60.
47. Illmensee, K., and Mintz, B. (1976) Totipotency and normal differentiation of single teratocarcinoma cells cloned by injection into blastocytes. Proc. Natl. Acad. Sci. USA 73:549-553.
48. Kauffman, S.A. (1971): Differentiation of malignancy to benign cells. J. Theor. Biol. 31:429
49. Mintz, B., and Illmensee, K. (1975) Normal genetically mosaic mice produced from malignant teratocarcinoma cells. Proc. Natl. Acad. Sci. USA 72:3585-3589.
50. Esteller, M. Epigenetics provides a new generation of oncogenes and tumor suppressor genes. 2006, British Journal of Cancer 94:179-183.

51. Jeong H.M, Kwon M, J, and Shin Y.K. Overexpression of cancer-associated genes via epigenetic derepression mechanisms in gynecologic cancer. 2014, Frontiers in Oncology 4:doi: 10. 3389/onc.2014.0012.

52. Terekhanova, N.V, Karpova, A, Liang W.W, Strzalkowski, A, Chen, S, Li, Y, et al. Epigenetic regulation during cancer transitions across 11 tumour types. 2023, Nature 623:433-441.

53. Ahuja, M.R. 1968. An hypothesis and evidence concerning the genetic components controlling tumor formation in *Nicotiana*. Molecular and general genetics 103:176-184.

54. Ahuja, M.R. (1998) Genetic tumors in *Nicotiana* and other plants. Quart. Rev. Biol. 73:439-462.

55. Knudson, A.G. (1971) Mutations and cancer: statistic study of retinoblastoma. Proc. Natl. Acad. Sci. USA 68:820-823.

56. Knudson, A.G. (1977) Genetic predisposition to cancer. In: Origins of Human Cancer. Hiatt, H.H., Watson, J.D., and Winston, J.A. (Eds). Cold Spring Harbor, New York, pp. 45-52.

57. Cleaver, J.E., and Bootsma, D.A. (1975) Xeroderma pigmentosum: biochemical and genetic characteristics. Ann. Rev. Gene. 9:19-38.

58. Kraemer, K.H, DiGiovanna, J.J. Xeroderma pigmentosum. 2023, In: Adam, M.P, Friedman, J, Mirzza, G.M. et al. Gene Reviews pp. 1-28.

59. Neel, J.V. (1971) Familial factors in adenocarcinoma of the colon. Cancer 28:46-50.

60. Engstrom, P.F., Rosvold, E.A., Boyd, N.R., and Orleans, C.T. (1996) Prevention of tobacco-related cancers. In: Cancer Medicine, 4th Edition. Holland JF, Frei, E.,

Bast, R.C., Kufe, D.W., Morton, D.L., and Weichselbaum, R.R. (Eds). Williams and Williams Publishing, Baltimore, pp. 447-463.

61. Fearon, E.R. (1997) Human cancer syndromes: Clues to the origin and nature of cancer. Science 278:10431050.
62. Sandberg, A.A., and Hossfeld, D.K., (1970) Chromosome abnormalities in human neoplasia. Ann. Rev. Med. 21:379-408.
63. German, J. (1972) Genes which increase chromosomal instability in somatic cells and predispose to cancer. Prog. Med. Genet. 8:61-101.
64. Rowley, J.D. (1977) Are nonrandom karyotypic changes related to etiologic agents? In: Genetics of Human Cancer. JJ Mulvihill, RW. Miller, JF Fraumeni, eds. Raven Press, New York, pp. 125-136.
65. Nowell, P.C., and Hungerford, D.A. (1960) A minute chromosome in human chronic granulocytic leukemia. Science 132:1497.
66. Mark, J. (1970) Chromosomal pattern in human meningiomas. Europ. J. Cancer 6:489-498.
67. Zhang, K.D. and Singer, H. (1967) Chromosome constitution of meningiomas. Nature 216:84-85.
68. Rowley J.D, The Philadelphia chromosome translocation- A paradigm for understanding leukemia. 1990, Cancer 65:2178-2184.
69. Olopede, O.L, and Rowley, J.D. Recurring chromosome rearrangements in human cancer. 1993, In: Cancer Medicine, Vol. 1. Holland, J.F, Frei, E, Bast, R.C, Kufe, D.W, Morton, D.L, and Weichselbaum, R.R. (eds). Lea & Febiger, Philadelphia, pp. 99-120.
70. Mitelman, F, and Levan, G. (1972) The chromosomes of primary 7,12-dimethylbenz(a)anthracene-induced rat sarcomas. Hereditas 71:325-334.

71. Levan, G., and Levan, A. (1975) Specific chromosomal changes in malignancy: studies in rat sarcomas induced by two polycyclic hydrocarbons. Hereditas 79:161-198.

72. Rudkin, G.T., Hungerford, D.A., and Nowell, P.C. (1964) DNA contents of chromosome Ph^1 and chromosome 21 in human chronic granulocytic leukemia. Science 144:1229-1231.

73. Ezdinili, E.Z., Sokal, J.E., Crosswhite, B.S., and Sandberg, A.A. (1970) A Philadelphia-chromosome-positive and -negative chronic myelocytic leukemia. Ann. Intern. Med. 72:175-182.

74. Whang-Peng, J., Canellos, G.P., Carbone, P.P., and Tjio, J.H. (1968) Clinical implications of cytogenetic variants in chronic myelocytic leukemia. Blood 32:755-766.

75. Hossfeld, D.K. (1974) Identification of chromosome abnormalities in the blastic phase of chronic myelocytic leukemia (CML) by Giemsa- and quinacrine-banding techniques. Humangenetik 23:111-118.

76. Rowley, J.D. A new consistent chromosome abnormality in chronic myelogenous leukemia identified by quinacrine and Giemsa staining. 1973, Nature 243:290-293

77. Ohno, S. (1971) Genetic implication of karylogical instability of malignant somatic cells. Physiol. Rev. 51:496-427.

78. Mariat, P, Michaux, J.L, and Rodhain, J. Philadelphia-negative (Ph^-) chronic myeloid leukemia (CML): comparison with Ph^+ CML and chronic myelomonocytic leukemia. 1991, Blood 78:205-211.

79. Kurzrock, R, Kantarjian H.M, Shtalrid, M, Gutterman, J.U, Talpaz, M. Philadelphia chromosome negative chronic myelogenous leukemia without

breakpoint cluster region rearrangement: A chronic myeloid leukemia with a distinct clinical course. 1990, Blood 75:445-452.

80. Jacobs, E.M., Luce, J.K., and Gailleau, R. (1966) Chromosomal abnormalities in human cancer: report of a patient with chronic leukemia and nonleukemic monozygotic twin. Cancer 19:869-876.

81. Goh, K.O., Swische, S.N., and Herman, E.C. (1967) Chronic myelocytic leukemia and identical twins. Arch. Intern. Med. 120:214-219.

82. Hethcote HW, Knudson AG (1978): A model for incidence of embryonal cancers: application to retinoblastoma. Proc. Natl. Acad. Sci. USA 75:2453-2457.

83. Knudson A.G. (1986). Genetics of human cancer. 1986, Ann. Rev. Genet.20:231-51.

84. Mark, J. (1973) Karyotype pattern in human meningiomas: a comparison between studies with G- and Q-banding techniques. Hereditas 75:213-220.

85. Zhang, K.D. Menigioma: a cytogenetic model of a complex benign tumor, including data on Cell Genetics 394 karyotyped cases. 2001, Cytogenetic Cell Genetics 93:207-220.

86. Mark, J. Chromosomal abnormalities and their specificity in human neoplasms: an assessment of recent observations by banding techniques. 1977, Advances in Cancer Research 24:165-222.

87. Heston, W.E. (1976) Genetic aspects of human cancer. Adv. Cancer Res. 23:1-21.

88. Mulvihill, J.J. (1977) Genetic repertory of human neoplasia. In: Genetics of Human Cancer. Mulvihill, J.J., Miller, RW, J.F., and Fraumeni, J.F. (Eds). Raven Press, New York, pp. 137-143.

89. Knudson AG, Strong LC, Anderson, DE (1973): Heredity and cancer in man. Progr. Med. Genet. 9:113-158.

90. Knudson, A.G. Mutation and cancer: A personal odyssey. 1995, Adv. Cancer Res. 67:1-23.

91. Orye E, Delbeke MJ, Vandenabeele B (1971): Retinoblastoma and D-chromosome deletions. Lancet 2:1376.

92. Wilson MG, Towner JW, Fujimoto A (1973): Retinoblastoma and D-chromosome deletions. Am. J. Human Genet. 25:57-61.

93. Haber DA, Hauseman DE (1991): Rate-limiting steps: the genetics of podiatric cancers. Cell 64:5-8.

94. Hansen MF, Cavenee WK (1988): Retinoblastoma and the progression of tumor genetics. Trends in Genet. 4:125-129.

95. Weinberg RA (1990): The retinoblastoma gene and cell growth control. Trends Biochem Sci. 15:199-202.

96. Lee EY-HP, To H, Shew J-W, Bookstein R., Scully P, Lee WH (1988): Inactivation of retinoblastoma susceptibility gene in human breast cancers. Science 241:218-221.

97. Hollingsworth REJ, Hensey CE, Lee W-H (1993): Retinoblastoma protein and the cell cycle. Curr. Opin. Genet. Devel. 3:55-62.

98. Knudson, A.G. Hereditary cancers disclose a class of cancer genes. 1989, Cancer 63:1888-1891.

99. Nishisho I, Nakamura Y, Miyoshi Y, Miki Y, Ando H, Horii A, Koyama, K, Utsunomiya J, Baba S, Hedge P, Markham, A, Krush AJ, Petersen G, Hamilton SR, Nilbert MC, Levy DB, Bryan, TM, Presinger AC, Smith KJ, Su L-K, Kinzler KW,

Vogelstein B (1991): Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science 253:665-669.

100. Powell, S.M. et al. 1992. *APC* mutations occur early during colorectal tumorigenesis. Nature 359:235-237

101. Su L-K, Vogelstein B, Kinzler K (1993): Association of the APC tumor suppressor protein with catenins. Science 262:1734-1737.

102. Fearon ER, Cho KR, Nigro JM, Kern SE, Simons JW, Rupert JM, Hamilton SR, Preisinger AC, Thomas G, Kinzler KW, Vogelstein B (1990): Identification of a chromosome 18q gene that is altered in colorectal cancers. Science 247:49-56.

103. Fearon, E.R. and B. Vogelstein. 1990. A genetic model for colorectal tumorigenesis. Cell 61:759-767.

104. Marx JL. (1993): New colon cancer gene discovered. Science 260:751-752.

105. Vogelstein B, Kinzler KW (1993): The multistep nature of cancer. Trends Genet. 9:138-141.

106. Braun AC (1969): The Cancer Problem: A Critical Analysis and Modern Synthesis. Columbia University, New York.

107. Sachs L (1986): Growth, differentiation and the reversal of malignancy. Sci. Am. 254(1):40-47.

108. Wolman SR, Holland AA (1975): Genetics of tumor cells. In: FF Becker, ed. Cancer: A Comprehensive Treatise. III. Plenum Publishing Corp. New York, pp. 155-188.

109. Kinsella AR, Radman M (1978): Tumor promoters induce sister chromatic exchanges: relevance to mechanisms of carcinogenesis. Proc. Natl. Acad. Sci. USA 75:6149-6153.

110. Lengauer C, Kinzler KW, Vogelstein B (1997): Genetic instability in colorectal cancers. Nature 386:623-627.

111. Breivik, J. 2005. The evolutionary origin of genetic instability in cancer. Seminar Cancer Biol. 15:51-60.

112. Holley, R.W. 1975. Control of mammalian cells in cell cultures. Nature 258:487-490.

113. Busch, H. 1976. A general concept for molecular biology of cancer. Cancer Res. 36:4291-4294.

114. Harris H., Miller OJ, Klein G, Worst P, Tachibana T (1969): Suppression of malignancy in cell fusions. Nature 233:363-369.

115. Harris, H. 1972. Cell fusion and analysis of malignancy. J. Nat. Cancer Inst. 48:851-864.

116. Stanbridge EJ, Wilkinson J (1978): Analysis of malignancy in human cells: malignant and transformed phenotypes are under separate genetic control. Proc. Natl. Acad. Sci. USA 75:1466-1469.

117. Scherr CJ (1996): Cancer cell cycles. Science 274:1672- 16:103-104.

Figure Legend

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 tumor (*Tu*) gene in a neoplasm. Initiation of carcinogenesis (B) involves genetic changes (mutational events) in the TS_I elements (represented by *TS'I* and these changes 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 (C1; represented by TS^{e}_{D}) then the developmental phase is potentially reversible. On the other hand, when TS_D genes involve mutational changes (C2; represented by TS'_D) then the developmental phase would be irreversible.

2025, Vol. 2
doi:10.x/journal.x.x.x