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# Role of Tumor Suppressor Genes in Carcinogenesis: A Narrative Review

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**ABSTRACT**

Oncological diseases represent a significant burden on individuals and society. Although the exact causes of cancer are not fully understood, evidence suggests that a combination of genetic, environmental, and lifestyle factors contribute to its development. Methods: This narrative review explores the role of tumor suppressor genes in carcinogenesis. An exhaustive literature search was conducted in electronic databases, selecting articles focused on genetic regulation by tumor suppressor genes for analysis. These genes play a crucial role in cell cycle regulation, DNA repair, and apoptosis, with significant implications for cell function and disease development. Abnormal patterns in these genes have been associated with neurological disorders and oncological diseases. Conclusion: Understanding the role of tumor suppressor genes in carcinogenesis provides insights into disease development and progression and offers opportunities to develop potential therapeutic strategies. However, studying genetic changes in carcinogenesis presents challenges, including the complexity of gene regulation and the heterogeneity of diseases. Nonetheless, the therapeutic potential of tumor suppressor gene regulation in cancer prevention is promising, and more research is needed to understand the underlying mechanisms and develop safe and effective treatments.

**KEYWORDS:** Tumor Suppressor Genes, Carcinogenesis, Gene Regulation, Apoptosis, Cell Cycle, DNA Repair, Mutations, Cancer Prevention.

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## INTRODUCTION

Tumor suppressor genes (TSGs) are vital genes that play a crucial role in controlling cell growth and proliferation. When functioning normally, these genes contribute to cancer prevention by regulating cell division, repairing DNA errors, and inducing apoptosis (programmed cell death) when cells are damaged beyond repair [1 2]

TSGs are genes that encode proteins that restrict cell proliferation and survival. Their loss of function due to mutations, dysregulation, or epigenetic alterations can contribute to the development and progression of cancer [2 3]

As for their overall functionality, TSGs function as critical regulators of cell cycle checkpoints, ensuring that genetic errors are rectified before a cell divides [1]They play a crucial role in DNA repair mechanisms, maintaining genomic integrity [1] TSGs play a prominent role in apoptosis; triggering cell death when genetic damage is irreparable [1] TSGs when inactivated through mechanisms such as hypermethylation, can result in uncontrolled cell growth, contributing to the development and progression of several types of cancer, including melanoma and breast cancer [3 2], TSGs are crucial regulators of normal cell physiology, and their impairment can lead to malignant transformation and cancer progression. Tumor suppressor genes (TSGs) play a critical role in preventing cancer development, known as carcinogenesis, through several mechanisms: Cell cycle regulation: TSGs control cell cycle progression to prevent uncontrolled cell proliferation, a characteristic trait of cancer cells. Alterations through mutations or dysregulation of TSGs can disrupt these regulatory functions, leading to aberrant cell growth [3] DNA repair: TSGs are often associated with DNA repair activity. Inactivity or loss of these TSGs due to epigenetic changes

such as hypermethylation can interfere with the DNA repair mechanism, leading to an accumulation of DNA damage, thereby promoting carcinogenesis [2 4] Apoptosis: TSGs induce programmed cell death or apoptosis in cells with severe DNA damage. Impairment of these genes can hinder apoptosis, allowing damaged cells to spread, contributing to tumor development [2 4] Inhibition of metastasis: Specific TSGs are associated with reduced cancer cell invasion or metastasis. For example, reduced expression of the CDH1 gene is significantly associated with an increased risk of tumorigenesis, suggesting its protective role in cancer development [5] In addition, as has been observed in several studies involving cancers such as breast cancer, cutaneous malignant melanoma, and squamous cell carcinoma of the head and neck, understanding and research of TSGs not only offer vital information about the mechanisms of carcinogenesis but also guide prevention and targeted treatment strategies [3 2 4]

## METHODOLOGY

This narrative review aimed to explore the role of tumor suppressor genes in carcinogenesis.

Literature search: An exhaustive search of electronic databases, including PubMed and other relevant sources, was conducted—the search aimed to identify articles published from the earliest available date to the present.

Search strategy: The strategy included the use of keywords and their combinations, such as:

Tumor Suppressor Genes, Carcinogenesis, Gene Regulation.

The inclusion criteria for the selection of articles were as follows:

Studies focusing on gene regulation by tumor suppressor genes in the context of carcinogenesis. Research involving human subjects or animal models. Studies that provide information on cell cycle regulation, DNA repair, or apoptosis. All articles are published in English.

The exclusion criteria were as follows:

Studies unrelated to tumor suppressor genes or carcinogenesis and studies conducted in non-human subjects or in in vitro models. Articles that did not provide relevant data or specific information on genetic mechanisms.

Two independent review authors assessed articles based on their titles and abstracts. Any discrepancies were resolved through discussion, and if no consensus was reached, a third reviewer was consulted. Full articles that met the inclusion criteria were obtained for detailed analysis.

Data extraction and synthesis: Data were extracted from selected articles to identify common themes and patterns related to regulation by tumor suppressor genes in carcinogenesis. Key findings and insights related to cell cycle regulation, DNA repair, and apoptosis were analyzed and summarized.

## THEORETICAL FRAMEWORK

Several tumor suppressor genes and their relationship to different types of cancer have been identified through various studies. According to one study, the rearrangement or dysregulation of tumor suppressor genes (TSGs) leads to molecular abnormalities that play an essential role in the development and progression of the disease [3] Oncogenes such as RAS, MYC, c-erbB-2, and BCL-2 are abnormally expressed. Usually, lower levels of tumor suppressor genes such as RB, p53, and p16INK4A are found. These irregularities could be used to develop diagnostics for the early detection of diseases and create gene therapy targets [6]- An increase in the uptake of FDG, a radioactive glucose compound used in PET imaging of cancers, has been observed in lung cancers where Rb, tumor suppressor genes p16, p27, and p53 have been altered [7] In head and neck squamous cell carcinoma (HNSCC) studies show a significant decrease in mitochondrial tumor suppressor genes such as SIRT3, SIRT4, and MTUS1. This downregulation, correlated with reduced mitochondrial DNA repair and increased proliferation (seen through an increased level of the proliferation marker Ki-67), is considered crucial in the progression of HNSCC [4] In cutaneous malignant melanoma: loss of function in tumor suppressor genes, primarily attributed to epigenetic alterations such as silencing by hypermethylation of the CpG island of the promoter, contributes to the progression of this type of cancer [2]

One study found that breast cancer patients with allelic loss at specific sites of tumor suppressor genes (1p34, 3p25, 8p22, 13q12, 17p13.3, or 17q21.1) had significantly higher five-year mortality rates, suggesting that these genes could predict prognosis and inform postoperative management [8]

Tumor suppressor genes (TSGs) are vital members of cellular regulatory networks and prevent uncontrolled growth through multiple mechanisms. Cell cycle regulation: TSGs play an essential regulatory role in the cell life cycle, often stopping the cycle to repair damaged DNA or to initiate cell apoptosis. For example, TP53 is a well-known regulator that can induce cell cycle arrest and DNA repair or apoptosis under stress conditions [1]Promote DNA repair: TSGs are actively involved in DNA repair pathways to maintain genomic integrity. The cell cycle arrests implemented by TSGs ensure that any damage is repaired before the cell progresses to the division stage. If repair is insufficient, the cell goes into apoptosis [1]Prevention of apoptosis: Some TSGs can regulate programmed cell death or apoptosis, helping to eliminate cells with extensive and irrevocable DNA damage. They promote cell survival under stressful conditions and limit uncontrolled growth. Indirect downregulation of genes: It has been observed that the p53 gene only activates transcription processes. Downregulation of specific genes due to p53 function is indirect and requires p21 [1]Mitochondrial energy metabolism: Mitochondrial genes such as SIRT3, SIRT4, and MTUS1 also behave like TSG and play an essential role in controlling cellular metabolism, reactive oxygen species (ROS) production, and apoptosis. Dysregulation of these

genes can increase cancer proliferation and progression [4]Epigenetic control: Finally, TSGs can be inactivated through epigenetic changes. For example, promoter hypermethylation can inactivate bona fide TSGs and influence melanoma progression. These mechanisms contribute to preventing uncontrolled cell growth. However, mutations or dysregulation of TSGs can lead to a loss of these protective functions and contribute to carcinogenesis [3].

Mutations in specific genes can contribute to cancer development when they result in a loss of function. Tumor suppressor genes can slow cell division, repair errors in DNA, and tell cells when to die. When such a gene is mutated, cells can continue to divide uncontrollably and not die when they should, leading to the formation of a tumor [6]. For example, in the RB gene, more than 90% of small cell lung cancers (SCLC) have detected abnormalities in RB, a vital regulator of the cell cycle [6]p53: p53 mutations are common in lung and oral cancer, with a frequency of up to 50% in non-small cell lung cancer (NSCLC) and 80% in SCLC [6], and 44% in oral squamous cell carcinoma [9]. This can lead to loss of function, cell proliferation, and inhibition of apoptosis [6] PALB2: 1.2% of patients with triple-negative breast cancer (TNBC) have deleterious mutations in this gene responsible for DNA repair processes [10] BAP1: Mutations in this gene may play a role in the development of kidney cancer [11], And some oncogenes promote cell growth and division. However, mutations in these genes can lead to their overexpression or permanent activation, resulting in high cell proliferation and potentially tumor formation [6]. For example, RAS mutations are observed in the K-RAS oncogene where it is permanently activated: up to 30% of adenocarcinomas show such mutations [6]MYC, this gene encodes a transcriptional activator, and mutations can adversely affect survival in small cell lung cancer (SCLC) [6]c-erbB-2: This growth factor receptor is overexpressed in up to 25% of NSCLC cases [6]BCL-2, a negative regulator of apoptosis, it is expressed differently in some NSCLCs due to mutations [6] 3. Non-coding RNA genes: Even though they do not produce proteins, their mutations can affect gene expression and subsequently stimulate cancer development [12]

**Interaction with other cellular pathways and their importance in cellular homeostasis.**

Tumor suppressor genes (TSGs) interact significantly with other cellular pathways and play a key role in maintaining cellular homeostasis. Based on the findings of several studies, here is an overview of TSG interactions and their importance. Role in DNA repair: The TP53 gene, recognized as a tumor suppressor, functions as a transcription factor. The TP53 mutation alters its response pathway and is critical for many cancers [1]. This research also points out that p53 targets genes involved in DNA repair, implying that TSGs play a crucial role in maintaining DNA integrity and stability. 2. Cell Cycle, Apoptosis, and Metabolism: High-confidence p53 target genes have been reported to be involved in multiple cellular responses, including cell cycle arrest, apoptosis, and metabolism, which are critical processes for maintaining cellular homeostasis [1] Energy metabolism: Mitochondrial TSGs such as SIRT3, SIRT4, and mitochondrial tumor suppressor 1 (MTUS1) are crucial in cellular energy metabolism. Loss or dysregulation of these genes, according to a retrospective study, is associated with unfavorable clinical outcomes in head and neck squamous cell carcinoma [4] Regulation of cell growth and proliferation, tumor suppressor genes affected by hypermethylation of the promoter's CpG island have been shown to encounter loss-of-function events, which promote the development and progression of cutaneous malignant melanoma (MBC). These genes precisely control cell proliferation and growth, and silencing induces uncontrolled growth and tumor formation [2] Feedback mechanism: Intricate feedback mechanisms are also incorporated, as seen with TP53 activating MDM2, which, in turn, induces p53 degradation, forming a negative feedback loop [13].

**Primary Mechanisms by Which Tumor Suppressor Genes Can Be Inactivated**

**Genetic mutations and their impact on gene function.**

Genetic mutations can lead to various impacts on gene function, including loss of function, alteration of function, or gain of new function. In some cases, genetic mutations can disrupt the normal function of the gene, leading to disease. For example, mutations in the dystrophin gene result in abnormal production of the protein dystrophin, which subsequently causes Duchenne muscular dystrophy (DMD). The severity and progression of this disease are related to the type and location of the mutation [14]In the case of cystic fibrosis (CF), mutations reduce, but do not eliminate, the function of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, contributing to the variant CF phenotypes. In some cases, factors other than CFTR mutations may result in clinical phenotypes that are indistinguishable from non-classical CF [15] Interestingly, specific germline polymorphisms may influence the risk of somatic mutations, as observed in a study on non-small cell lung cancer (NSCLC). These polymorphisms may favor cellular malignancies, thereby increasing susceptibility to specific somatic mutations, such as EGFR tyrosine kinase mutations [16]Genetic mutations may not always result in noticeable alterations in both the gene product and disease severity, as observed in a study of filaggrin gene mutations (FLG) and atopic dermatitis (AD). In specific individuals with mutations in the FLG gene, AD severity, skin water content, and transepidermal water loss were not affected [17]. In addition, mutations in the genes of sarcomeres are often responsible for hypertrophic cardiomyopathy (HCM). The clinical implications of these mutations may vary, as people with mutations in the sarcomere gene experience worse lifelong outcomes and more frequent lethal arrhythmic events [18]. In general, the effects of genetic mutations are diverse and highly dependent on the specific gene, the type of mutation, and the type of cell involved. They can significantly inform disease risk, diagnosis, prognosis, and treatment.

**Epigenetic silencing and its role in the inactivation of tumor suppressor genes.**

Epigenetic silencing plays a critical role in the inactivation of tumor suppressor genes. This process affects the development and progression of several types of cancer, including cutaneous malignant melanoma and pituitary adenomas. Here is how it works: Methylation in selected genes: The scientists observed that epigenetic silencing of multiple tumor suppressor genes, such as SOCS1, SOCS2, RASSF1a, CDKN2a, and MGMT, occurs frequently in the formation of melanoma #16374457. In the case of pituitary adenomas, alterations were found in at least 24 specific genes, including CDKN2A, GADD45y, FGFR2, caspase-8, and PTAG [19]. These genes showed abnormal DNA methylation in more than 50% of pituitary adenoma samples, resulting in tumor suppressor gene silencing and tumorigenesis. CpG island methylator phenotype (CIMP): Evidence suggests the existence of a common subset of promoter CpG islands that are hypomethylated in standard samples but become hypermethylated in cancer, establishing a link between hypermethylation and gene silencing in cancer [20]. However, this hypermethylation does not always result in a decrease in gene expression. Histone deacetylation: Overexpression of histone deacetylases (HDACs) induces epigenetic silencing of tumor suppressor genes. The use of HDAC inhibitors has been shown to increase antitumor activity in several studies, bolstering the role of epigenetic silencing in cancers [21].

In summary, epigenetic silencing through DNA methylation and histone deacetylation plays a vital role in the inactivation of tumor suppressor genes. It contributes to the development and progression of cancers by silencing tumor-specific suppressor genes, leading to uncontrolled cell proliferation and tumor growth. However, more research is needed to fully understand the intricate interplay between epigenetic modifications and gene expression in cancer [20].

**Chromosomal deletions and their relationship to the loss of tumor suppressor genes.**

Chromosomal deletions have been found to involve the loss of tumor suppressor genes that usually reside in those loci, which may play a critical role in the development and progression of several types of cancer. Multiple studies provide strong evidence for this: One study suggested that there may be a tumor suppressor gene on chromosome 1p associated with colorectal cancer, as allelic loss in regions 1p36 and 1p32 was found to be an independent predictor of poor prognosis in patients with adenocarcinoma of the colon [22]Similar findings have been reported in cases of breast cancer, where patients with allelic loss at 1p34, 3p25, 8p22, 13q12, 17p13.3, or 17q21.1 had significantly higher risks of postoperative mortality compared to those whose tumors retained both alleles at those loci [8]. In particular, allelic losses at 1p34-36 in a tumor were found to serve as a negative prognostic indicator, which could guide the postoperative management of patients with 10955803 breast cancer. In a study involving patients with small cell carcinoma and lung adenocarcinoma, a very high incidence of allelic deletions at different chromosomal loci was observed in small cell carcinomas, especially on chromosomes 3p, 13q, and 17p. Adenocarcinomas also showed a high frequency of loss of heterozygosity on chromosome 3p 2892196. Analysis of bladder tumors identified four regions on chromosome 9 whose deletion was associated with a high risk of recurrence, highlighting a link between chromosome 9 abnormalities and recurrence of superficial bladder cancer [23] A study on colorectal carcinoma observed that patients with nm23-H1 allelic deletions on chromosome 17q21 were three times more likely to develop distant metastases compared to patients without such deletions [24]. Overall, these results emphasize that specific chromosomal deletions are linked to the loss of tumor suppressor genes, leading to increased cancer progression and poor prognosis.

**Role of genetic inheritance in the transmission of mutations in tumor suppressor genes.**

Inherited mutations in tumor suppressor genes can contribute significantly to the development of several types of cancer, including colorectal, breast, ovarian, and pediatric cancer. In a study involving 1120 pediatric cancer patients, germline mutations were identified in 8.5% of patients. Specifically, these mutations were often found in the TP53, APC, BRCA2, NF1, PMS2, RB1, and RUNX1 genes. Interestingly, a family history of cancer did not predict the presence of an underlying predisposition syndrome in most of these patients, indicating that genetic factors may be independent of family history in some cases [25]. A review of hereditary breast and ovarian cancer syndrome (HBOC) found that mutations in the BRCA1 and BRCA2 genes are responsible for most cases of HBOC. Lifetime cancer risks for mutation carriers are 60-80% for breast cancer and 20-40% for ovarian cancer. In addition to BRCA genes, mutations in other susceptibility genes, such as the Fanconi anemia (FA) group, mismatch repair (MMR) group, DNA repair group, and other tumor suppressor genes, may also predispose to HBOC [26]. In a cohort study of 44 patients with Hodgkin's disease with second malignancies (SMNs), only a tiny portion carried germline mutations in TP53 and BRCA2. While it confirms that such mutations may contribute to secondary tumorigenesis, it also suggests that the incidence of these mutations may be relatively low among patients with SMN [27]. In a large population-based association study, inherited defects in genes involved in base cleavage repair (BER), a mechanism for maintaining genome integrity, were shown to contribute to the incidence of colorectal cancer. Biallelic defects of MUTYH had a 93-fold increased risk of colorectal cancer and accounted for 0.54% of the entire cohort.

Interestingly, even heterozygous carriers of the >55-year-old MUTYH mutation had a 1.68-fold increased risk of colorectal cancer, indicating a role for heterozygous mutations in cancer predisposition in adulthood [28]. In conclusion, genetic inheritance can contribute significantly to the transmission of mutations in tumor suppressor genes, which can increase an

individual's risk of developing certain types of cancer. The role of genetic inheritance in cancer predisposition is supported by the observed increased risk of cancer among carriers of specific mutant alleles.

Genetic counseling and testing can play an essential role in managing cancer risk for people with a family history of cancer: 1. Improved risk perception and decision-making: As evidenced by a study involving Ashkenazi Jews [29], genetic counseling helps improve general knowledge of cancer genetics. It improves understanding of personal behavior, the meaning of positive and negative test results, the mechanisms of cancer inheritance, and physician knowledge. This increased understanding helps people identify and make informed decisions, such as opting for genetic testing or lifestyle modifications. 2. Accurate Risk Assessment: According to a Systematic Review [30], five reference models accurately estimate the individual risk of BRCA mutations. Genetic counseling helps people accurately assess the likelihood of being carriers of a genetic mutation that increases the risk of cancer. 3. Emotional well-being: Genetic counseling has also been found to decrease cancer-related worry, anxiety, and depression [30]. It allows people to cope with the emotional aspects of being at risk. 4. Guided Medical Provisions: The results of genetic testing can often influence medical management. In a retrospective review of the medical records of 670 at-risk patients who underwent genetic testing [31], positive results increased surveillance in 96% of patients with deleterious mutations. Conversely, negative results in people under surveillance for a known familial mutation led to decreased risk and reduced subsequent surveillance and treatment. 5. Family Planning: Parents with a personal history of cancer usually express interest in genetic counseling/testing [32], primarily since it could provide vital information about their children's cancer risk. 6. Improved Lifelong Care: For families considering genetic testing for children [33], genetic counseling and testing could provide critical information about the family's cancer risk across the lifespan and prepare them for potential future medical decisions.

**Tumor-specific suppressor genes and their relationship to particular types of cancer**

**BRCA1 and BRCA2 in breast and ovarian cancer.**

The BRCA1 and BRCA2 genes are tumor suppressor genes associated with a significantly increased risk of breast and ovarian cancer. These genes are mainly involved in DNA repair processes, and their mutation has been widely studied for its implications in cancer predisposition. According to an observational study that placed information from 19,581 BRCA1 mutation carriers and 11,900 BRCA2 mutation carriers, it was found that the specific mutation type and location within BRCA1/2 were associated with different breast and ovarian cancer risks. The study established breast cancer group regions (BCCRs) and ovarian cancer group regions (OCCRs) within these genes. Mutations within certain regions resulted in an increased risk of breast or ovarian cancer, indicating a direct correlation between the location and type of mutation and the type of cancer developed [34]. Women who carry BRCA1 or BRCA2 mutations have a lifetime risk of breast and ovarian cancer of 60-80% and 20-40%, respectively. The remaining cases of hereditary breast and ovarian cancer syndrome (HBOC) that are not attributed to BRCA mutations may involve other cancer susceptibility genes, such as the Fanconi anemia (FA) group, mismatch repair (MMR) group, and other DNA repair or tumor suppressor genes [26]. Patients carrying a mutation in a BRCA gene who develop cancer in one breast have an increased risk of developing cancer in the other breast, depending on the specific gene mutated and the patient's age during the illness. Prophylactic bilateral mastectomy and adnexectomy significantly reduce the incidence of breast and ovarian cancer in these high-risk individuals [35]. It is also worth noting that the presence of BRCA mutations can extend beyond breast and ovarian cancers. In a systematic review and meta-analysis, a significant increase in the frequency of mutations in BRCA1 and BRCA2 was observed in patients with colorectal cancer, suggesting that these genes may also contribute to colorectal cancer risk [36]. Through these findings, it appears that the relationship between specific tumor suppressor genes and cancer types is not only proportional but also located within these genes and can significantly affect susceptibility [34 35 26 36].

**TP53 and its relationship with various types of cancer.**

The TP53 gene, known as the tumor suppressor gene, has shown significant associations with several types of cancer: Adenocarcinoma and squamous cell carcinoma of the cervix: A systematic review found a higher frequency of TP53 gene mutation in adenocarcinoma of the cervix (13.3%) compared to squamous cell carcinoma (5.9%) [37]. Patterns of TP53 mutations in these two cervical cancers showed significant geographic variation, with the highest frequency of TP53 mutation in cervical adenocarcinoma observed in Asia. In particular, different mutation patterns were observed: three codons (175, 248, and 273) were commonly mutated in both types of cancer, one codon (249) mainly in squamous cell carcinoma and another (282) only in adenocarcinoma. Breast cancer: The research found no significant overall associations between common genetic variations in TP53 and breast cancer risk [38]. However, mutations in TP53 have been shown to produce a significantly poorer survival outcome in both node-negative breast cancer and node-positive breast cancers. In both subgroups, the TP53 mutation was found to be a possible independent marker of poor prognosis [39]. Colorectal cancer: In a study involving 1,060 patients with colon and rectal cancer, TP53 was associated with more aggressive tumor behavior. The relationship between TP53-altered tumor cells and energy balance was explored, and a possible modifying effect on the patient's body mass index was observed [40]. Bladder cancer: The literature has suggested that the TP53 mutation, regardless of stage, may be predictive of outcome in bladder cancer. In this case, one study found

exposure-specific heterogeneity in TP53 pathway inactivation. A higher prevalence of TP53 inactivation was found among hair dye users and men with at-risk occupations. At the same time, evidence showed a relatively lower TP53 mutation and alteration in bladder cancers of individuals with higher arsenic exposure [41]. Overall, the TP53 mutation plays a crucial role in different types of cancer, and the impact appears to differ depending on the specific type of cancer and, potentially, the individual's lifestyle factors. More studies are needed to understand better the role of TP53 alterations in these cancers and their impact on prognosis and outcomes.

**APC in colorectal cancer.**

The adenomatous polyposis coli (APC) gene plays a vital role in colorectal cancer. As a tumor suppressor gene, its mutation is commonly considered an early event in colorectal cancer tumorigenesis [42]. A mutation in APC was found in fecal DNA obtained from patients with early colorectal tumors, indicating its role in the early stages of the disease [43]. The presentation and risk of colorectal cancer may vary depending on the specific APC gene variants found. For example, a case-control study conducted in Taiwan identified three novel mutations in the APC gene that were associated with colorectal cancer risk in Taiwanese subjects, including a deletion at codon 460 leading to a frameshift and two missense mutations [42]. However, the APC mutation site does not appear to predict survival in patients with familial adenomatous polyposis who have colorectal cancer [44].

Interestingly, relatively high folate intake was positively associated with colorectal tumors carrying APC mutations among men. It suggests that folate may enhance colorectal carcinogenesis via an APC-mutated pathway [45]. A meta-analysis revealed that three APC-specific polymorphisms (D1822V, E1317Q, and I1307K) influenced the risk of colorectal neoplasia [46]. In summary, the APC gene is integral to the pathogenesis of colorectal cancer. The type of mutation may influence the risk and presentation of the disease, but it does not appear to predict the outcome of the disease. In addition, certain dietary factors, such as folate intake, could interact with APC mutations to influence disease risk [42] [43] [44] [45] [46].

**Current Challenges in the Study and Treatment of Cancer Related to the Inactivation of Tumor Suppressor Genes**

The study and treatment of cancers related to the inactivation of tumor suppressor genes poses several challenges: 1. Complexity of tumor suppressor genes: Tumor suppressor genes (TSGs) have various functions in normal cellular function. Mutation and dysregulation lead to aberrant molecular processes in cancer cells, greatly complicating the understanding of their roles in the oncogenic process [3]. 2. Detection of aberrations in tumor suppressor genes: Many alterations, such as hypermethylation leading to silencing of TSGs, are common in cancers such as melanoma [47], but detecting these changes remains a challenge. Variability in detection methods and a lack of standardized protocols can affect the accuracy of results. 3. Epigenetic alterations: TSGs can be inactivated not only by genetic alterations but also by epigenetic modifications, most commonly promoting hypermethylation of the CpG island. Determine the functional role of such alterations in the progression of cancers such as cutaneous malignant melanoma [48]. It is complex and remains a significant focus of research. 4. Drug specificity: Several studies investigate potential new oral drugs such as TAS-117 in cancer patients with altered tumor suppressor genes. However, the development of targeted therapies that can disrupt specific signaling pathways is technically challenging and requires extensive clinical trial testing to determine their efficacy and safety [49]. 5. Loss of function: In addition to inactivation, loss of mitochondrial TSG expression has been linked to unfavorable clinical outcomes in cancers, making the recovery of their function critical. However, this loss of function is a complex process to reverse [4]. 6. Mutations in the p53-MDM2 interaction: In approximately 50% of all human cancers, the tumor suppressor protein p53 is inactivated by mutation, making attempts to reactivate it by directing its interaction with MDM2 a significant focus of research. However, the identification and development of specific inhibitors remains a complex task [13]. 7. Limited knowledge about oncogenic signaling pathways: TSGs are involved in multiple signaling pathways. Comprehensive analysis of these pathways and mutations in advanced thyroid cancers using next-generation sequencing improves understanding of these tumors for targeted therapies. However, significant work is still required to fully characterize these pathways and their interactions to determine the best treatment approach [50].

**Emerging Strategies to Fight Cancer Associated with Inactivation of Tumor Suppressor Genes**

Emerging strategies and potential targeted therapies to fight gene-associated cancer, such as inactivating tumor suppressor genes, include gene therapy, gene editing, and suicide gene therapy.

According to a phase I clinical trial, CT-guided intratumoral gene therapy is a practical alternative treatment approach for non-small cell lung cancer. Patients underwent CT-guided intratumoral injections of a tumor suppressor gene, p53, resulting in gene transfer in 50% of treated patients. Four weeks after treatment, four of the six patients showed stable disease at the site of the treated tumor [51]. In addition, in a progressive trial for head and neck cancer, gene therapy was carried out with a lipid vector containing the HLA-B7 gene and the beta2 microglobulin gene. Treated patients demonstrated no adverse effects of gene therapy, with increased apoptosis observed in tumors that responded, indicating the efficacy of this method [52].

Gene editing using the CRISPR/Cas9 system has shown promising results by characterizing genes and exploring different mechanisms involved in tumorigenesis. This method makes it possible to tailor strategies based on intrinsic factors such as cancer type, gene function, mutation type, and

various technical approaches [53]. The use of CRISPR/Cas9 gene-editing technology in combination with chimeric antigen receptor T (CAR-T) cell therapy has demonstrated improved function and reduced toxicity in animal models of different types of cancer, including acute leukemia, glioma, and melanoma [54]. According to a review of the literature, suicide gene therapy involves the delivery of genes to cancer cells that convert non-toxic prodrugs into active chemotherapeutic agents, effectively resulting in a behavior change that is fatal to the cancer cells. This strategy has been effective in cell cultures, laboratory animals, and in some early clinical trials [55].

In light of the immediate success of these therapies, future studies are anticipated to focus on reducing unintentional bias, improving the long-term persistence of edited cells, and mitigating delivery and dosing challenges [54 56]. Advances in the delivery of tissue- and cell-specific suicide genes using specific promoters are also expected to improve the clinical applicability of suicide gene therapy [55]. Current research is expanding to exploring different genes and disease mechanisms, optimizing strategies for different types of cancer, refining technical approaches, and improving CAR-T cell therapies with gene editing [53 54]. Gene therapies work best when the brain is not the primary target. In addition, early intervention is more effective, so it could be beneficial to target the presymptomatic stage [56]. Finally, combination therapies, such as integrating gene therapy with traditional cancer treatments (chemotherapy, radiation, etc.), could also be a direction for future cancer treatment research.

**Implications for public health and cancer prevention**

Understanding tumor suppressor genes (TSGs) and their roles in oncogenic processes is critical for cancer prevention and treatment [3]. They play an integral role in cellular energy metabolism, apoptosis, and free radical generation, and their dysregulation may aid cancer progression [4]. In public health and cancer prevention, understanding the functions and mechanisms of TSGs has several implications: - Diagnostic and prognostic markers: Alterations such as mutations or epigenetic modifications in TSGs, such as methylation, could serve as potential diagnostic and prognostic markers. One study showed that serum SOCS1, SOCS2, RASSF1a, CDKN2a, and MGMT were hypermethylated in 41 melanoma patients [47]. Dysregulated expression of SIRT3, SIRT4, and MTUS1, along with the DNA repair gene OGG1-2a and increased proliferation, have shown potential prognostic significance in head and neck squamous cell carcinomas (HNSCC) [4]. Targeted therapies: Understanding tumor suppressor pathways may inspire the development of targeted therapies. TAS-117, an investigational oral drug, targets parts of cell signaling that may be overactive due to the inactivation of the tumor suppressor protein PTEN [49]. Health education and behavior modification: Knowledge of TSG mutations could lead to recommendations for lifestyle adjustments for people with a family history of cancer, as these mutations can be inherited. Risk prediction and detection: Identifiable modifications or mutations in TSGs may suggest increased vulnerability to specific cancers. This can inform risk prediction models and lead to more informed detection strategies. It is important to note that there is still much to understand about TSGs, particularly given the inconsistencies between individual genetic studies and high-throughput research [1]. Therefore, continued research on TSGs is crucial for fully realizing these implications.

## CONCLUSION

Research on tumor suppressor genes (TSGs) is crucial for cancer prevention and treatment, with comprehensive studies highlighting the role of TSGs in the oncogenic process, particularly in breast cancer [3]. - Some genes such as SIRT3, SIRT4, and MTUS1, described as mitochondrial tumor suppressor genes, are critical in multiple types of cancer, including head and neck squamous cell carcinoma (HNSCC). Dysregulation of these genes has been linked to decreased mitochondrial DNA repair and increased cancer cell proliferation, making them potential targets for future treatments [4]. - Epigenetic alterations, such as hypermethylation of the promoter CpG island, have been linked to loss-of-function events in TSGs, contributing to the progression of cutaneous malignant melanoma. Further study of these alterations could provide valuable tools in cancer diagnosis, prognosis, and possibly targeted therapy [48]. - Promoter methylation in TSGs plays a vital role in thyroid carcinogenesis. It is crucial to conduct more research to understand how it interacts with other risk factors to develop effective prevention and treatment strategies [5]. - The finding of a germline-somatic link in carcinogenesis represents a promising clue. Genetic variation in loci encoding "driver kinases" involved in carcinogenesis, such as DYRK2 and CDKL2, could be crucial for understanding the molecular basis of breast cancer risk and progression [57].

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