

DEFENDER OF THE GENOME: UNRAVELLING THE MECHANISM OF TUMOR SUPPRESSOR GENES (tsgs)

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ABSTRACT

So, it's almost to our knowledge that tumor suppressor genes (TSGs) which makes the cell division slow and functions the cell that when they will die. They are regulating processes like DNA damage repair, checking the cell cycle and genomics stability etc. Inactivation or mutations of these genes play a critical role in cancer growth because they result in the loss of regulatory mechanisms, allowing for unregulated cell division and genetic damage accumulation. Suppose a mutation inactivates a tumor suppressor gene, the protein it encodes is either not generated or does not function effectively, which can result in uncontrolled cell division. If we talk about the complex mechanisms of TSGs which are evaluated in this study, recognition is given to crucial members such as TP53, RB1, BRCA1/BRCA2 and PTEN. In this review, there's a more about the various classes of TSGs into caretakers, gatekeepers, and landscapers by illuminating their functions into various cellular pathways. On top of that, new and modified medication options for TSG pathways, including as gene therapy and synthetic lethality are in the process of establishment. Therefore, we get a better understanding

of TSGs mechanism and mutational changes which assists the progress for better cancer diagnostics, prognosis, and precision therapy.

Keywords: *Cancer, gene therapy, genomics, tumor suppressor genes, synthetic lethality*

1. Introduction

We all know that cancer is increasing day by day. In this area the tumor suppressor genes as genome's guardian by controlling the oncogenic transformations. Genes accountable for these were found and classified as "oncogenes." Although "antioncogenes" have been introduced, there has been a lack of definitive evidence for years. In the year 1969, Knudson gave a prediction that existence of tumor suppressor genes (TSGs) based on the development of inherited and sporadic retinoblastomas (Knudson et al., 1993). In 1986, the retinoblastoma (RB1) gene was effectively cloned, supporting his postulated "2-hit" hypothesis for carcinogenesis (Knudson et al., 1971). Inactivation of tumor suppressor genes usually results in a phenotype when both copies are lost. In cancer, inactivating one copy of a TSG causes loss of the remaining copy, followed by emergence. One cannot overstate the importance of TSGs for maintaining cellular integrity. Most relevantly we see the reaction to unusual growth signals, genotoxic stress and other carcinogenic impulse, acting as genomic soldiers. Understanding the molecular mechanisms of TSGs, classifying them, and taking into account their importance for cancer treatment are the main goals of this review. By comprehending these pathways, scientists and medical professionals can create customized treatments to lessen the effects of TSG inactivation in cancer. Kinzler and Vogelstein classified TSGs into two categories: "gatekeeper" genes and "caretaker" genes (Kinzler et al., 1997). Caretaker genes maintain genomic integrity, whereas gatekeeper genes control how cells grow or divide. Understanding the distinctions between these two gene types is critical for developing treatment approaches. Nowadays, practically all molecular targeted therapies block oncogenes such as kinases Kinase inhibitors are among the most effective cancer treatments ever developed (Kinzler et al., 2004). Through

this review let's emphasize and explore the molecular mechanisms, classification, and therapeutic implications which are related to tumor suppressor genes.

2. Mechanisms of Tumor Suppressor Genes (TSGs)

2.1 Regulation of Cell cycle

Tumor suppressor genes such as RB1 and CDKN2A are very much crucial for regulating the G1/S checkpoint. The retinoblastoma protein (pRB), which is encoded by the RB1, allows to bind and inhibits E2F transcription factors, therefore it prevents transcription of genes which is required for S-phase entry (Weinberg et al., 1995). When the loss occurs in RB1 function is because of different mutations that aggregate in the preceding cell proliferation (Knudson et al., 1971). One more key regulator, is CDKN2A, which encodes p16INK4a and this protein also inhibits the cyclin-dependent kinase 4/6 (CDK4/6), averting the phosphorylation of pRB and securing that cells do not prematurely advance throughout the G1 phase. Deprivation of CDKN2A function, frequently through deletion or promoter methylation, is a hallmark of many cancers (Sherr & McCormick et al., 2002).

2.2 DNA Damage Response (DDR) and Repair

One of crucial gene TP53, it encodes for p53, which is a central regulator for DDR. If we talk about DNA damage, then p53 accumulates and operates the transcription of targeted genes, including GADD45 for repair, CDKN1A (p21) for cell cycle arrest, and pro-apoptotic genes like BAX (Levine, 1997; Vousden & Prives, 2009). In over a half of the human population with cancer, mutations are found in TP53, impair the DDR and allows the cells to heap up genetic abnormalities (Kandoth et al., 2013).

2.3 Apoptosis

When the process of cellular damage becomes irreparable then TSGs open a door for promoting apoptosis. We can also see that PTEN antagonizes the PI3K/AKT pathway in a subtle way, by vanquishing anti-apoptotic signals and which promotes cell death (Cantley & Neel et al., 1999). After, PTEN decreases, it gives rise to increased survival

signaling which contributes to the tumorigenesis (Salmena et al., 2008). Additionally, there are BAX and BCL2-associated pathways that are regulated through p53 to initiate various mitochondrial-mediated apoptosis (Chipuk et al., 2004).

3.Classification of Tumor Suppressor Genes

So, the tumor suppressor genes (TSGs) play an important and very crucial role in generating cellular processes and preventing excessive cell development, which is one of the characteristics of cancer. Hence, these genes are divided into three categories: caretakers, gatekeepers, and landscapers, they have their unique roles in maintaining the genomic stability and altering the tumor microenvironment. They also help in regulating cell proliferation.

3.1 Caretaker

Here, the tumor suppressor genes help to polish up cohesion of genome by finding and reconstructing the DNA damage. Then it ensures the chromosomal stability, and prevents mutation, which can lead to oncogenesis. Their primary function is to act as “genomic defenders,” safeguarding the fidelity of genetic material.

If we look upon the significance there are genes like BRCA1 and BRCA2. These genes are very crucial and essential for the homologous recombination repair pathway, which is exact mechanism for rebuilding of DNA double-strand breaks. When BRCA1 or BRCA2 function is disapproved, cells proceed to error-prone ways such as non-homologous end joining (NHEJ), which increases genomic instability and the probability of mutations. The occur of germline mutations in BRCA1 or BRCA2 likely increases the risk of hereditary breast and ovarian cancer (Venkitaraman et al., 2002). Lack of these genes also causes exposure to DNA-damaging drugs, which is the base for medicines like PARP inhibitors.

3.2 Gatekeeper

In this, the tumor suppressor genes are straight away involved in supporting the cell growth and apoptosis. These genes act as “brakes” on cell proliferation, not allowing cells from dividing fastly or surviving irreversible harm. Let’s

give a look towards PTEN that how it works. It is a negative selector of the PI3K/AKT pathway, PTEN conquers cell for survival and proliferation. Its reduction aims to unchecked activation of this pathway, assisting to tumor growth. Now here comes RB1. The RB1 gene is well known for encoding the retinoblastoma protein (Rb), as it regulates the G1/S checkpoint of the cell cycle. Therefore, when RB1 is mutated, cells bypass through this checkpoint and enters the S phase without proper growth control (Lane et al., 1992).

3.3 Landscaper

Here the tumor suppressor genes affect the tumor microenvironment by ensuring correct tissue architecture and extracellular matrix integrity. While they do not directly govern cell proliferation, their absence produces a favorable environment for tumor development.

If we see the loss of APC that leads to aberrant activation of Wnt signaling, promoting the heaping of β -catenin in the nucleus and driving unidentified cell division. APC mutations are a hallmark of familial adenomatous polyposis (FAP) and sporadic colorectal cancers (Polakis et al., 2000).

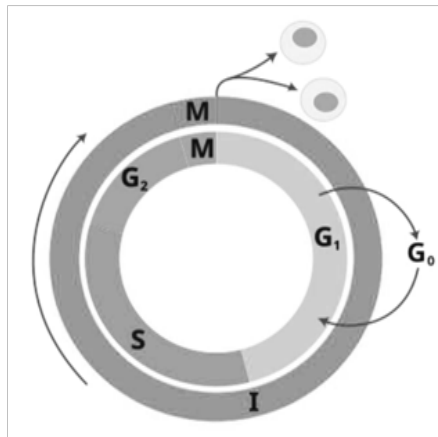


Figure:1

4. Different functions and mutational patterns in Tumor Suppressor Genes (TSGs)

As we know, so much about the mechanism of Tumor suppressor genes (TSGs). It plays a crucial role in preventing tumorigenesis by regulating cell cycle arrest, maintaining apoptosis, and promoting genomic integrity.

4.1 Genetic Mutations

Tumor suppressor genes (TSGs) genetic mutations include point mutations, nonsense mutations, and frameshift mutations, all of which sometimes result in the growth of shortened or non-functional proteins. The missense mutations in TP53, one of the most essentially researched TSGs, they mostly alter the DNA-binding domain etc. These mutations interrupt the transcriptional control of downstream genes involved in apoptosis, DNA repair, and cell cycle arrest (Soussi et al., 2007). There are few other TSGs, such as RB1 (retinoblastoma protein), are frequently deactivated by nonsense or frameshift mutations, resulting in impaired cell cycle control (Knudson et al., 1971).

4.2 Epigenetic Silencing

The transcriptional silencing in TSGs is due to epigenetic changes, methylation of DNA and alteration of histone. As CDKN2A promotes hypermethylation, which encodes p16^{INK4a}, is a widespread route of inactivation in hostility such glioblastoma, melanoma, and large cell of lung cancer. When the silencing occurs, it distracts the RB pathway, permitting for unlimited cellular generation (Herman et al., 1995). Now let's look into epigenetic suppression of the BRCA1 through promoter methylation, which has been seen in breast and ovarian cancer by various, that hinders the homologous repair and become the cause to genomic instability (Esteller et al., 2000). Afterwards these epigenetic changes are unique and reversible, making them main targets for diagnosis like DNA methyltransferase and histone deacetylase inhibitors.

4.3 Loss of Heterozygosity (LOH)

So, loss of heterozygosity is a commonly caused in cancer, which results the lack of the second allele of a tumor suppressor

genes through different actions like deletion of chromosomes, mitotic recombination, or uniparental distomy. In TP53 loss of heterozygosity is a well-documented event in cases such as lung and breast cancer, it assists co-occurring of mutations in the left over allele (Malkin et al., 1990). On the other hand, loss of heterozygosity in the RB1 locus is seen in retinoblastoma and osteosarcoma, which highlights the role of carcinogenesis (Harbour et al., 1988). After performing studies, it's noticed that LOH is a critical "second hit" in the Knudson two-hit hypothesis, which states that both alleles must be inactivated for tumor growth (Knudson et al., 1971).

5. Therapeutic Process

There are various therapies introduced. By the help of tumor suppressor gene modifications has been noticed in cancer treatment. All this type of therapy includes techniques like gene therapy, targeted therapies and also immunotherapy.

5.1. Targeted therapies

The good effects created by tumor suppressor genes deficits caused in cancer cells is used in therapies. A very well-known example is synthetic lethality, where the cancer cells with few mutations are specifically destroyed by targeting compensating processes. For example, BRCA1/2-mutant cancers, they have deficits in homologous recombination repair, so they are in extremely exposure to PARP inhibitors. These inhibitors hampers the base excision repair mechanism, resulting in DNA damage reconstruction and cell death (Farmer et al., 2005). These modified and precised medicine techniques have indicates great success in treating BRCA-mutant breast and ovarian cancers.

5.2. Gene Therapy

Gene therapy is one of the best ways for curing cancer and also it is better than chemotherapy and radiotherapy. Its working is, it mainly aims to reimpose the working of inactivated Tumor suppressor genes and then activates them. It is also a practicable treatment approach and reaching to many peoples. Gene therapy is considered of the safest method. Now let's take example of adenoviral vectors

with a functional TP53 gene, they have showed promisable results in preclinical and early clinical trials for diagnosis of non-small cell lung cancer (Martins et al., 2006). While they have promising results, challenges still remain, including as productive delivery to tumor cells and prevailing over immune responses. New modifications in delivery technologies, such as nanoparticle-based vectors, are also looked over to intensify therapeutic efficacy and safety (Kaiser et al., 2018).

5.3. Immunotherapy

Immunotherapy is made to strengthen our immune system so that it's fight cancer more effectively. It engages the immune system to fight cancer and overcome it, so that it can help to reduce the effect for loss of tumor suppressor genes. Mutations that occur in TSGs, likely TP53, subsequently leads to the generation of neoantigens, which are main peptides seen on the tumor cell surface. T-cells can target these neoantigens, following in immune-mediated cancer cell death as it destroys them. Immune checkpoint inhibitors, likely PD-1/PD-L1 blockers, have been productive in exploiting these neoantigens to boost and magnify anticancer immunity. Immunotherapy is essential treatment option in TSG-mutated cancers because it promotes the immune system's ability to acknowledge and attack cancer cells and destroys them.

6. Conclusion

So, this is the mechanism of the tumor suppressor genes. When the inactivation, caused due to mutations, different epigenetic changes, or loss of heterozygosity, they result in the lack of these protective mechanisms and enhances tumor growth. It is a helpful process. As we got to know about the regulation of cell cycle, the DNA damage response and apoptosis etc. Tumor suppressor genes such as TP53, RB1, PTEN, and BRCA1/2 indicates the diversity of function and critical functions these genes play in cell control. By understanding the molecular mechanisms of TSGs has provided insights into cancer biology while also opening up new treatment approaches. Synthetic lethality, targeted gene therapy, and immunotherapy use the vulnerabilities generated by TSG loss to selectively eradicate cancer cells while preserving healthy

tissues. Despite these gains, obstacles remain, particularly in restoring TSG function and overcoming resistance to treatments. So, we should concentrate on creating novel therapeutic techniques, leveraging developments in gene editing, and investigating the tumor microenvironment's role in TSG regulation. A better understanding of TSGs will improve our ability to create precise, effective medicines, eventually benefiting cancer patients.

7. Future Prospective

The study of mechanism of tumor suppressor genes (TSGs) tells us about the future-comings of cancer research, diagnostics, and therapeutics. It focuses on the advanced genomics and personalized Medicine. Many advancements are seen in genomics, gene editing, and computational biology are likely to revolutionize our understanding of TSGs functions and their role in cancer prevention and progression. Gene-editing tools like CRISPR-Cas9 offer immense potential for restoring TSG function in cancer cells. TSGs such as APC and PTEN are known to influence the tumor microenvironment. Future research may focus on manipulating the microenvironment to inhibit tumor growth and metastasis. TSGs and their regulatory pathways offer potential as biomarkers for early cancer detection and prognosis. Several areas of focus are emerging as key directions for future exploration.

8. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationship that could have appeared to influence the work reported in this paper.

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