Pan-African Journal of Health And Psychological Sciences
ISSN: 3093-4737 | www.pajhps.org
Vol.2, Issue 2 | April-June 2026

Role of the TP53 Gene in Cancer Progression and Therapeutic Strategies

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Abstract

TP53 gene is an important tumor suppressor gene that is central to ensuring genomic stability and inhibit cancer development. It also codes the p53 protein, which is a transcription factor that controls vital cellular functions like cell cycle arrest, apoptosis, DNA repair, and senescence. In healthy physiological states, p53 is a kind of protective system against genetic damage by inhibiting the development of abnormal cells. Nevertheless, one of the most frequent genetic changes in a large number of human malignancies is the mutation or inactivation of the TP53 gene resulting in the loss of its tumor-repressive properties. This review focuses on the structural and functional aspects of the TP53 gene, highlighting its role in regulating cellular homeostasis and safeguarding genomic integrity. It also focuses on how TP53 mutations promote cancer development, such as unregulated cell growth, apoptosis resistance, and increased metastatic capabilities. The review further addresses the

ISSN: 3093-4737

different treatment interventions that address TP53, including gene therapy, small molecule drugs, and novel interventions, including CRISPR-based gene editing and immunotherapy. Nevertheless, issues like diversity of mutations, drug resistance, and limits to delivery still exist. Thus, further studies are necessary to come up with more effective targeted therapies using TP53 and enhance clinical outcomes in cancer treatment.

Keywords: TP53 gene, p53 protein, cancer progression, tumor suppression, gene mutation, apoptosis, targeted therapy

1. Introduction

Cancer is a complicated and multifactorial illness that is defined by uncontrolled cell increase, apoptotic resistance and capacity to spread and proliferate to different areas. It is formed as a result of genetic and epigenetic changes that interfere with the normal processes of cell regulation. The processes that are impacted as a result of these changes include cell cycle control, DNA repair and signal transduction [1]. The environmental factors such as carcinogens and radiation, and genetic predisposition are also a major contributor to cancer. The progressive accumulation of these abnormalities leads to loss of normal growth control. Knowledge of the molecular pathogenesis of cancer is pivotal in determining the key regulatory genes and developing targeted therapies that are effective in preventing and managing malignant transformation [2].

1.1 Overview of Cancer

Cancer is a complex disease which is defined by uncontrolled cell division, cell death resistance and invasion of tissues around, as well as metastasis to other organs. It occurs as a result of accumulation of genetic and epigenetic changes, which interfere with normal cellular homeostasis. These changes influence important

ISSN: 3093-4737

regulatory processes that are engaged in cell cycle regulation, apoptosis, DNA repair, as well as signal transduction [3]. Carcinogens, radiation, lifestyle habits and infections are some of the environmental factors that contribute to cancer development, as well as inherited genetic mutations. Genomic instability is a hallmark of cancer, it allows cells to mutate and develop tumor features. There are various defense mechanisms present in normal cells to avoid such abnormalities but in cancerous cells, these mechanisms are usually impaired [4]. TP53 gene is one of the most significant regulatory genes that help to preserve the genomic integrity. This gene is mutated or inactivated in a big percentage of the human cancers. Most cancers have a series of stages, such as initiation, promotion, and progression, which are caused by genetic changes. Sustained proliferation, angiogenesis, immune evasion, and resistance to therapy are some of the abilities acquired by tumors as they develop. These are the main basics of cancer biology that are necessary in order to discover molecular targets and to plan effective therapeutic strategies [5].

1.2 Importance of TP53 Gene

One of the most important tumor suppressor genes in human biology that plays a significant role in the prevention of cancer development is the TP53 gene. It contains the p53 protein that is a transcription factor that regulates genes that deal with cell cycle arrest, apoptosis, DNA repair, and senescence. Because of the critical role it plays in genomic stability, p53 has been described as the guardian of the genome [6]. In physiological conditions, the level of p53 is low in the cell. But when the cell is subjected to stress like DNA damage, hypoxia or the activation of oncogenes, p53 is stabilized and activated. It then causes cell cycle arrest, giving time to repair the DNA, or causes apoptosis in case of irreparable damage [7]. This defense system inhibits the spread of genetically abnormal cells. TP53 gene mutations are seen as one of the most frequent genetic changes in cancers causing the loss of the tumor-

ISSN: 3093-4737

suppressive effect of the gene. Mutant p53 proteins can even acquire oncogenic property that facilitates

tumor development and therapy resistance in some instances [8]. TP53 is not just a tumor suppressor, but it has an important impact on the response to treatment and prognosis. Thus, the TP53 pathways are one of the primary areas of interest in the design of new anticancer drugs and precision medicine interventions [9].

2. Structure and Function of TP53 Gene

TP53 gene is found in chromosome 17p13.1 and it codes the protein that is a transcription factor called p53. It is composed of functional domains such as transactivation, DNA-binding and oligomerization domains, which are all critical in its functionality. The DNA-binding domain allows p53 to regulate genes that regulate the cell cycle and apoptosis, and the protein is a tetramer to be active [5]. P53 has a functional role in ensuring genomic stability by acting in response to cellular stressors including DNA damage, hypoxia and activating oncogenes. It controls target genes causing cell cycle arrest, repair of DNA or apoptosis, thus preventing the growth of damaged cells and stabilize cellular homeostasis [10].

2.1 Gene Structure

TP53 gene is approximately 20 kb in size and has 11 exons. It codes a protein that consists of several functional domains and 393 amino acids. The N-terminal transactivation domain mediates the onset of transcription of target genes and the central DNA-binding domain facilitates sequence-specific binding to DNA. C-terminal domain plays a role in regulatory processes and protein-protein interactions [11]. The mutations often take place in DNA-binding domain resulting in a defective regulation of genes as shown in (**Fig. 1**). The gene structure is very conservative indicating its importance in defense mechanisms in the cells. Its activity is also controlled by alternative splicing and post-translational modifications. It is crucial to

ISSN: 3093-4737

comprehend the structure of the genes since any structural changes have a direct effect on the p53 activity and play a role in the cancer process [12].

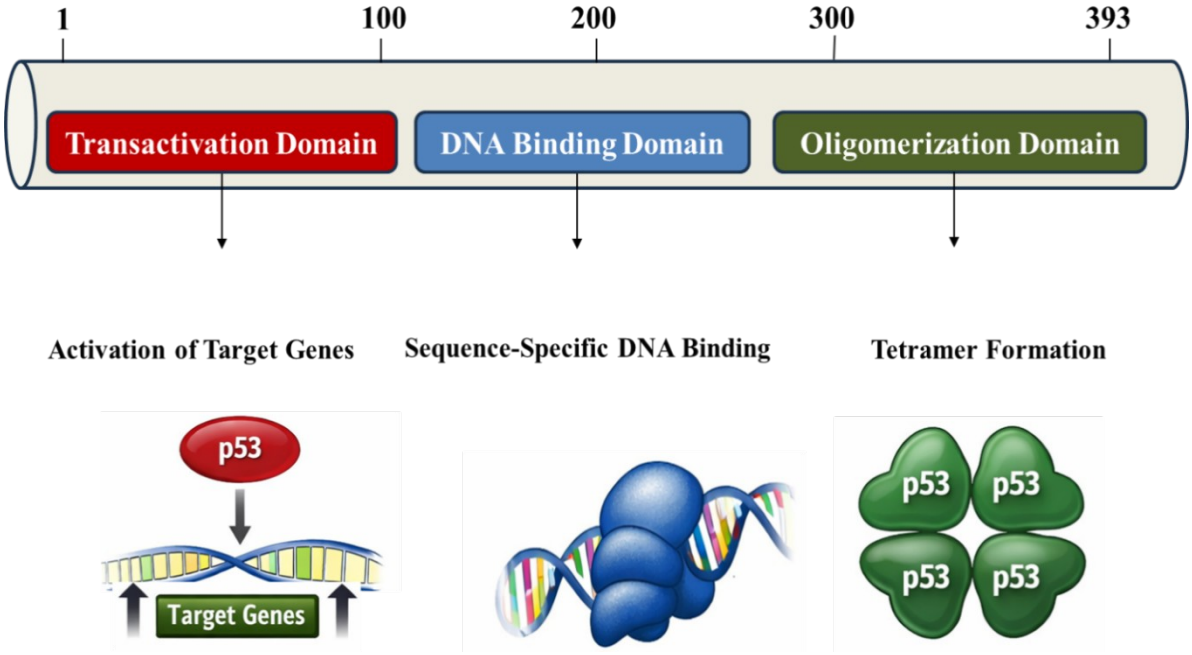

Figure 1: Structure of p53 Protein

Caption: *Structural domains of p53 protein showing transactivation, DNA-binding, and oligomerization regions essential for its function.*

2.2 Biological Functions of p53 Protein

The p53 protein which is a product of the TP53 gene is the key element in ensuring cellular integrity. It is a transcription factor which regulates genes related to cell cycle arrest, apoptosis, senescence and DNA repair. DNA damage will pause the cell cycle at G1/S, which will provide time, enabling the repair mechanisms to operate, when there is p53 present [13]. In case of irreparable damage, p53 triggers apoptosis, getting rid of potentially toxic cells. It also helps in senescence which is a permanent growth arrest. Moreover, p53 plays a role in the control of metabolism, oxidative stress and angiogenesis. By all these various roles, p53 has averted the occurrence of

ISSN: 3093-4737

mutations and inhibited the growth of tumors, which is why it is crucial in cancer prevention as mentioned in (**Table 1**) [14].

Table 1: Functions of p53 Protein

Sr. No.	Function	Role of p53	References
1.	Cell Cycle Arrest	Stops cell cycle at G1/S checkpoint	[15]
2.	DNA Repair	Activates repair genes to fix damaged DNA	[16]
3.	Apoptosis	Induces programmed cell death	[17]
4.	Senescence	Causes permanent cell cycle arrest	[18]
5.	Angiogenesis	Inhibits formation of new blood vessels	[19]

3. Role of TP53 in Cancer Progression

TP53 gene is an important gene that helps in preventing the progression of cancer by controlling cell growth and ensuring genomic stability. In healthy cells, p53 plays the role of a protective measure against malignancy. In most types of cancer, however, TP53 has been mutated or inactivated, and it loses its protective properties. This enables proliferation of cells that have failed DNA to go out of control leading to tumor formation [20]. The mutant p53 proteins can also acquire functions that can enhance tumor growth, metastasis and resistance to therapy as shown in (**Fig. 2**). TP53 gene changes are frequent in many cancer types and have been connected with bad prognosis and fast tumor development, which underscores their significance [21].

ISSN: 3093-4737

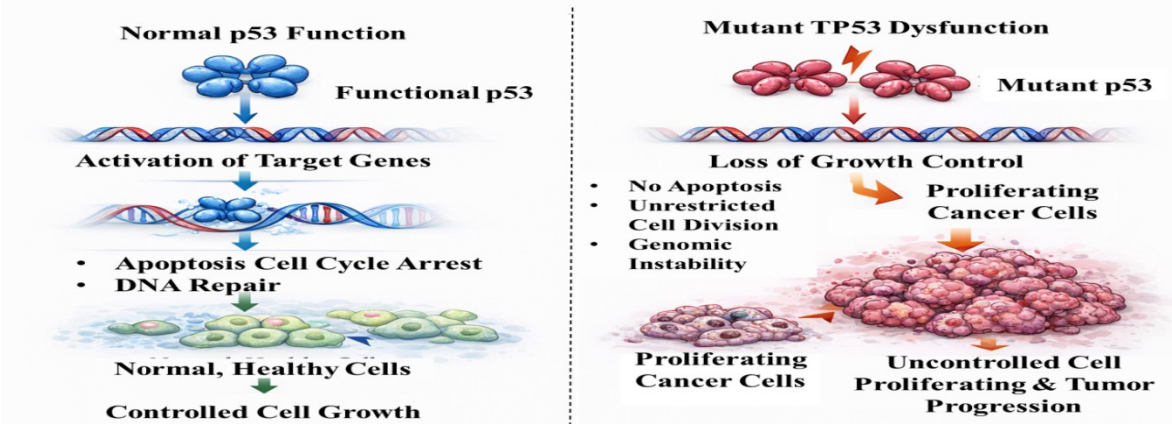

Figure 2: Role of TP53 in Cancer Progression

Caption: *Comparison of normal p53 function and mutant TP53 leading to uncontrolled cell proliferation and tumor progression.*

3.1 TP53 Mutations in Cancer

The TP53 gene has the highest prevalence of genetic changes in human cancers. The mutations usually take place in the DNA-binding domain thus affecting the capacity of p53 in controlling target genes. The majority of mutations are missense mutations which cause a defective protein with less or different functioning [6]. Other mutant variants of p53 do not only lack the ability to suppress tumors, but also develop an oncogenic phenotype allowing them to promote the development of cancers. These gain-of-function mutations have the capability to promote cell proliferation, invasion and apoptotic resistance. TP53 mutations are typical of breast, lung, and colorectal cancer. They are frequently linked to adverse clinical outcomes and a decrease in response to treatment, which is why they are crucial biomarkers in cancer diagnostics and treatment [22].

3.2 Mechanisms of Tumor Suppression

TP53 gene has a tumor-suppressive effect in various ways. Among its main functions are the induction of cell cycle arrest in case of DNA damage to enable repair

ISSN: 3093-4737

processes to restore genomic integrity. This inhibits proliferation of mutated cells. p53 also induces apoptosis by triggering pro-apoptotic genes in situations where the cell cannot repair cell damage [17]. It also causes senescence which is a permanent cell cycle arrest that prevents cell proliferation, p53 also controls angiogenesis by preventing the development of new blood vessels that enable the growth of tumors. With such mechanisms, p53 functions as a vital obstacle to the development of cancer. TP53 loss or mutation can lead to the disruption of these protective pathways, allowing tumor cells to develop and survive in adverse conditions [23].

3.3 Loss of Function and Tumor Development

One of the key contributors to tumor development is the loss of functionality of the TP53 gene. In case of mutation or deletion of TP53, cells lose control over the cell cycle, DNA repair and apoptosis. This leads to accumulation of genetic abnormalities and heightened genomic instability. In the absence of functional p53, the damaged cells keep on dividing causing uncontrolled proliferation and formation of tumors [5]. In other instances, mutant p53 proteins mediate with other tumor suppressor pathways which further induce cancer progression. Mutation of p53 is also linked with the resistance to chemotherapy and radiation therapy, which is based on apoptosis to kill cancer cells. Therefore, dysfunction of the TP53 is a major factor contributing to the development and disease advancement of cancer [24].

4. Therapeutic Strategies Targeting TP53

Targeting the TP53 gene has become a major focus in cancer therapy due to its high mutation frequency in various cancers. It has a promising therapeutic potential through the restoration of its normal operation or the regulation of its pathways. Several approaches such as gene therapy, small molecule drugs and targeted approaches are being pursued to deal with TP53 dysfunction. These treatments are

ISSN: 3093-4737

designed to either reactivate mutant p53, or increase its tumor-suppressive properties, or to kill cells that do not express p53 [24]. The current innovations in the field of molecular biology and pharmacology have allowed the creation of agents that repair or replicate the activity of p53. Even though the obstacles like drug resistance and delivery issues remain, attacking TP53 will be a major step to changing the outcomes of cancer treatment and enhancing personalized medicine as shown in (**Table 2**) [25].

Table 2: Therapeutic Strategies Targeting TP53

Sr. No.	Strategy	Mechanism	Example/Approach	References
1.	Gene Therapy	Restores normal TP53 function	Adenoviral p53 delivery	[26]
2.	Small Molecule Drugs	Reactivate or stabilize p53	MDM2 inhibitors	[27]
3.	Immunotherapy	Targets p53-deficient cancer cells	Immune checkpoint approaches	[28]
4.	Gene Editing	Corrects TP53 mutations	CRISPR-Cas9	[29]

4.1 Gene Therapy Approaches

Gene therapy is geared towards repairing the normal functionality of the TP53 gene by placing a functional copy of the gene into cancer cells. This is carried out by utilizing viral vectors, like the adenoviruses, to insert the TP53 gene into tumor tissues. The re-expressed p53 can cause cell cycle arrest or apoptosis in cancer cells, thus preventing tumor growth [30]. Among them is recombinant p53-based therapies that have demonstrated positive outcomes during clinical trials. Nevertheless, there are still issues

ISSN: 3093-4737

of effective delivery, immunogenicity, and low specificity of targeting. Even with these shortcomings, gene therapy is an effective approach to curing TP53-related cancers [31].

4.2 Small Molecule Drugs Targeting p53

Small molecule drugs that interact with p53 are expected to repair or improve the activity of TP53 gene. The compounds have the ability to reactivate mutant p53 proteins, stabilize wild-type p53, or inhibit negative regulators like MDM2. These drugs stimulate apoptosis and prevent tumor growth by restoring the activity of p53 [32]. A number of small molecules are in the process of exploration and have demonstrated promise in preclinical and clinical trials. This technique is especially

effective in those cancers with mutant TP53, but it remains structurally intact. Small molecule therapy has the benefits of being easily administered and of acting with specificity, and so is a promising field of research in cancer pharmacotherapy [11].

4.3 Emerging Therapies

The new treatment options in the context of the TP53 gene are associated with the innovative therapies based on immunotherapy, CRISPR gene editing, and individualized medicine. The mechanisms behind these strategies are to specifically attack the TP53 mutated cancer cells with minimal effects to normal cells. The CRISPR technology has a prospect to directly repair TP53 mutations on the genetic level [29]. The goal of immunotherapy methods is to improve the immune system to identify and destroy p53-deficient cancer cells. Also, personalized medicine incorporates genetic profiling to customize therapeutic interventions according to the presence of TP53 mutation. Such innovative treatments are the future of cancer treatment but more research is required to make them safe and effective [33].

5. Challenges and Future Perspectives

ISSN: 3093-4737

Although there is a lot of progress, there are still a few obstacles to target the TP53 gene in cancer treatment. TP53 mutations are highly variable and its biological effects are complicated, so it is hard to create universal treatments. Also, the constraints of drug resistance, inefficient delivery mechanisms, and off-target effects decrease the success of therapy. Subsequent studies need to be aimed at a greater understanding of the molecular pathways of TP53 mutations and the creation of more specific and tailored treatment. Gene editing, targeted drug development and personalized medicine innovations are promising directions. Moreover, TP53-based therapies could be used in combination with conventional treatments to improve clinical outcomes. Further studies are needed to exploit the therapeutic potential of TP53 in cancer treatment.

6. Conclusion

TP53 is an important tumor suppressor gene that is critical in ensuring stability of the genome and prevention of cancer. Its capacity to control cell cycle arrest, apoptosis, DNA repair and senescence is crucial in the regulation of abnormal cell proliferation. Nevertheless, one of the most frequent mutations and inactivation of TP53 in human-cancer cells cause a loss of its protective activities and facilitate tumor growth, metastasis, and resistance to therapy. Recent breakthroughs in molecular biology have prompted the emergence of a wide range of therapeutic approaches, such as gene therapy, small molecule drugs, as well as new ones, such as gene editing and immunotherapy. Although such improvements are made, there are still issues like variances of mutations, drug resistance, and limitations of delivery. Thus, further investigation is needed to gain a deeper insight into TP53 pathways and create more effective, targeted, and personalized cancer treatments to achieve better clinical results.

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