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General *P53* Signaling Pathway-Related Genes in Cancer

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Abstract
Over the past 50 years, cancer research has significantly improved, starting with identifying the initial oncogene, a gene responsible for promoting cancer development. Cancer frequently involves disrupting molecular signaling pathways that govern cellular growth and differentiation. The *P53* signaling pathway performs a fundamental function in the cellular stress response and is responsible for controlling the cell cycle, DNA repair, and apoptosis. The fault of this pathway has been associated with various types of cancer, making it a principal field of research in the study of molecular biology and the medicine of cancer therapy. The goal of this research is to thoroughly and precisely review and study the general *P53* signaling pathway and its associated genes, including *TP53*, *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, and *TP53BP1*. Obtaining information concerning the mechanisms and functions of these genes in the general *P53* biopathway can provide valuable knowledge of the important progressions of cancer and the advance of new treatment approaches. Herein, we provide an up-to-date review of general *P53* signaling pathway-related genes in cancer to better understand the molecular complexity underlying cancer research.

Keywords: Cancer, General *P53* signaling pathway, *TP53*, *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, *TP53BP1*

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Introduction

Cancer is expected to overtake cardiovascular illnesses worldwide, with an estimated 13 million cancer-related deaths and over 21 million new cases anticipated by 2030.[1] The COVID-19 pandemic has postponed and hindered cancer diagnosis and therapy due to the closure of healthcare facilities, disruptions in employment and health insurance, and concerns regarding potential exposure to COVID-19.[2] Cancer is a pathological condition characterized by cells' unregulated proliferation and growth,[3,4] primarily attributed to genetic modifications in specific genes. Over the past decade, there has been a notable advancement in DNA sequencing technology, enabling the systematic investigation of genetic alterations. Numerous studies have achieved significant advancements in several domains of cancer research with the aim of comprehending the underlying causes of its carcinogenic process.[5] Nevertheless, there is still a significant lack of understanding about the specific pathways involved in the development of cancer. Consequently, our comprehension of the frequently implicated mechanisms and signaling pathways has improved.[6,7] With the increasing number of genetic alterations that specific drugs can effectively target, integrating DNA sequencing into routine clinical care is becoming more prevalent. Nonetheless, a notable diversity exists in the genetic makeup and pathways affected among various tumor types and individual tumor specimens. Consequently, it is imperative to comprehensively comprehend the genes and pathways that undergo alterations in all types of cancer. *P53* is the most prevalent mutated gene in human malignancies, particularly in relation to tumor suppression. There is a clear link between tumor development and the dysfunction brought on by *TP53* mutations.[8] *P53*, acting as a protector of the genome, has been shown to exert effects on several cellular processes, including cell metabolism, ferroptosis, tumor microenvironment, and autophagy. These mechanisms, together, contribute to the suppression of malignancies.[8] The general *P53* signaling pathway is a vital regulatory mechanism that performs a significant function in upholding cellular homeostasis and preventing the progression of diseases such as cancer.[9] This pathway encompasses a complex system of molecular interactions that regulate crucial physiological processes, including DNA repair, apoptosis, senescence, and cell cycle arrest, in reaction to various biological stresses.[9] The *TP53* gene performs a vital role in the *P53* signaling pathway since it is responsible for producing P53 (also

named tumor protein 53 or TP53) as a transcription factor. The primary role of the TP53 protein is to control many pathways, including cell cycle arrest, DNA repair, cell apoptosis, autophagy, metabolism, ferroptosis, stem cell differentiation, senescence, and the tumor microenvironment.[10] Additionally, it plays a crucial role in determining cell survival or death in stressful situations. When *P53* is turned on, it controls the transcription of numerous target genes that are affected by apoptosis, DNA repair, and control of the cell cycle. Several genes are closely associated with the major or general *P53* signaling biopathway and contribute to its overall functioning, including *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, and *TP53BP1*. MDM2 functions as an E3 ubiquitin ligase, leading to the degradation of P53. This interaction has a role in controlling the amounts and functioning of P53. MDM4 inhibits the transcription capacity of P53. It functions as a suppressor of *P53* activity and plays a role in maintaining precise control over P53 levels.[9] *CDKN2A* is a gene that inhibits the growth of tumors and produces two significant proteins, p16INK4a (known as p16 or multiple tumor suppressor 1) and p14ARF (also called ARF tumor suppressor). These proteins are needed for the control of the cell cycle and the process of senescence. *CDKN2B* is a tumor suppressor gene responsible for encoding the p15INK4b protein. This protein also plays a role in controlling the cell cycle and the process of senescence. TP53BP1 is a protein that binds to P53 and exerts a role in DNA repair mechanisms. It has a function in preventing the integrity of the genetic material and inhibiting the building of harm to the DNA.[9] These interactions create a feedback loop that tightly regulates P53 levels and activity. The study of molecular biology has witnessed substantial progress in recent decades, thanks to fast breakthroughs. These advancements have led to great leaps in understanding essential biomacromolecules that are fundamental to the development and progression of diseases. This review gives an in-depth look at the general *P53* signaling pathway linked to the growth and spread of cancerous tumors, a significant cause of illness and death worldwide. This discussion is critical because it explains several key signaling molecules involved in developing cancerous tumors. This review study provides a comprehensive overview of the general *P53* signaling pathway-related genes (i.e., *TP53*, *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, and *TP53BP1*).

The Conceptual Progress of the Hallmark Capabilities of Cancer

The hallmarks of cancer encompass distinct biological features driving malignancy development. Original features include ongoing signaling for cell division, avoiding growth inhibitors, stimulating angiogenesis, starting invasion and metastasis, preventing cell death, and allowing cells to replicate and live forever. Enabling factors, such as deregulating cellular energy and avoiding immune destruction, support these hallmarks. Additionally, emerging hallmarks such as tumor-promoting inflammation and genome instability contribute to the evolution and progression of cancer. Understanding these hallmarks enables the development of more targeted, effective cancer therapies.[3] Figure 1

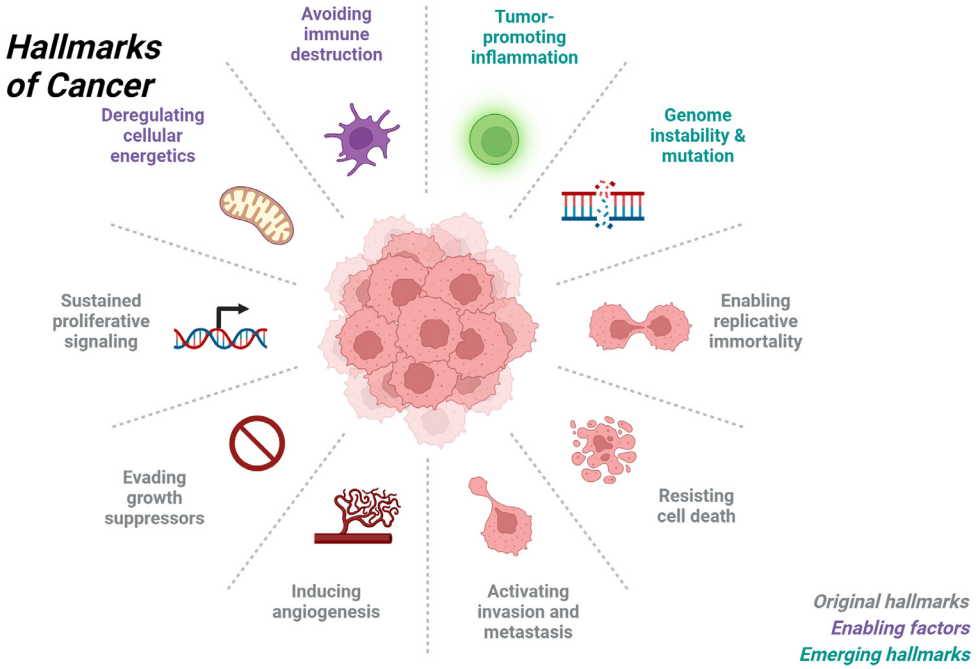

Figure 1. The Six Characteristics Unique to Cancer Working Together to Make Tumors Grow and Spread to Other Body Parts (Metastasis) Continue to be a Reasonable Basis for Understanding How Cancer Works. *Source*. Created with BioRender.com: Confirmation of Publication and Licensing Rights with agreement number: NH26VFY1ED

illustrates the fundamental characteristics called the "Hallmarks of Cancer". This illustration encapsulates the six fundamental capabilities.

General *P53* Signaling Pathway

Maintaining genome integrity is a crucial determinant in ensuring the production of healthy and disease-free daughter cells, which contribute to the formation of homogenous and healthy tissues engaged in a wide range of biological processes. Therefore, it is often observed that genomic instability is a causative factor in the development of several disorders, such as cancer. Regulating genomic instability is widely recognized as a well-established characteristic of cancer development.[11] However, it is essential to note that human cells include intricate and highly effective defensive systems. These mechanisms play a crucial role in safeguarding the genome and ensuring its integrity in the face of many internal and external factors that have the capability to trigger harm to DNA. The group of defensive mechanisms that respond to DNA damage is often referred to as DNA damage response pathways.[12,13] The tumor suppressor protein p53 exhibits activity in the central node of the DNA damage response. The tumor suppressor *P53* is at the top of the list of guardians of genome substrate.[12] The *TP53* gene has the highest frequency of mutations in human malignancies. *TP53* mutations cause cellular abnormalities that contribute to the development of tumors. The primary function of the p53 protein is to serve as a transcription factor, exerting regulatory control over a diverse scale of cellular processes, comprising cell cycle arrest, DNA repair, cell apoptosis (the result of an arranged intracellular waterfall of genetically regulated phases),[10] autophagy, and metabolism. Additionally, it exerts a vital role in verifying cell fate in situations of stress.[10] Over the course of time, an increasing body of studies has shown the intricate and interrelated nature of the p53 pathway. The P53 pathway has provided insights into metabolic homeostasis, the immunological microenvironment, stem cell biology, and other disciplines. However, the presence of mutant p53 may induce alterations in its DNA binding affinity, conformational structure, and thermal stability and ultimately compromise the effectiveness of p53.[10] The p53 protein functions as a transcription factor, exhibiting both nuclear and cytoplasmic localization. It has a particular affinity for DNA binding and is of critical importance in terms of controlling several genes. In typical circumstances, the cellular levels of the P53 protein are upheld at a low level due to the stringent regulation exerted by its negative regulators, MDM2 and MDMX. These regulators facilitate the breakdown of p53 via a process called ubiquitination.[14] The process of p53 ubiquitination is hindered when cells encounter various stressors, both from inside the cell and from the external environment, such as DNA damage, hypoxia, food deprivation, and the danger of cancer cell formation. As a result, there is a prompt elevation in the cellular levels of the p53 protein. Several posttranslational changes, including phosphorylation, acetylation, and methylation, facilitate the activation and stabilization of accumulated p53. The p53 protein, when stabilized, undergoes tetramerization inside the nucleus. Then, it interacts with certain DNA sequences, modulating gene transcription and subsequently influencing the downstream of several signaling pathways.[10] The complicated P53 response is influenced by both cell type and environment. It accelerates the process of cell death by activating the senescence and apoptosis pathways while simultaneously promoting cell survival by halting the cell cycle and repairing DNA.[14] This route is often regarded as the most effective and reliable method for preventing cancer. P53 may also trigger apoptosis via the transcription-dependent or transcription-independent method. The activation of *P53* upregulates the expression of genes involved in both intrinsic and extrinsic apoptosis pathways while promoting cell death. The mentioned genes include the P53-upregulated modulator of apoptosis (*PUMA*), *BAX* (Bcl-2-associated X protein), *BID* (BH3-interacting domain), and *NOXA* (Phorbo-12-myristate-13-acetate-induced protein 1). It specifically focuses on mitochondrial outer membrane permeabilization, which is a critical component of the innate apoptotic process. This occurs without the process of transcription.[10] On the other hand, senescence is a significant consequence of the activation of *P53* due to broken telomeres and cellular stress. Senescent cells are live and working cells that cannot be undone and do not make more copies of themselves. Under normal circumstances, cells usually experience senescence due to telomere shortening after a certain number of replication cycles. Nevertheless, a range of conditions, such as DNA damage and the activation of oncogenes, may trigger senesces in cells, resulting in a process referred to as stress-induced premature senescence.[14-16] The cyclin-dependent kinase (CDK) inhibitor p21 modulates p53-induced stress-induced premature senescence. The p21 protein is synthesized by the *WAF1/CIP1* gene, which is a tumor suppressor gene situated on chromosome 2.6p21.[17] This gene is also known as part 1 of wild-type p53/protein 1 reactive to CDK. The intended protein has been established to have a connection with the cellular cycle. The activation of p21 is a well-observed process that leads to growth suppression in various physiological contexts, such as aging, Alzheimer's disease, and amyloidosis.[17] If p21 is turned on for a long time, it may cause p16INK4A to be turned up, which could activate the retinoblastoma pathway senescence program.[18] P53 also stabilizes PAI-1, a hallmark of senescent cells, to directly cause senescence. Several studies indicate that ionizing irradiation causes senescence, not apoptosis, in several cancer cell lines. Another common p53 response to cellular stress is

promoting and modulating cell cycle arrest and DNA repair. It is generally known that p53 inhibits cell cycle progression and activates p21. When cell cycle progression stops, p53 activates several DNA repair pathways.[18] The tumor suppressor protein p53 has the ability to trigger cell death in a sustained manner upon exposure to various cellular stressors.[9] Nevertheless, there remains an unresolved inquiry into the factors that govern the diverse responses elicited by p53. The complete understanding of the elements that influence the p53-induced response, such as the cell type, microenvironment, kind of stress, and degree of damage, needs thorough clarification.[9] TP53 mutations in cancers are prevalent and have tumor suppressor activity, making them attractive targets for tumor treatment. However, drug development against p53 has been hindered by its specificity, lack of a drug-binding pocket, and difficulty in restoring function. Despite these challenges, scientists are optimistic about attacking this challenging pharmacological target.[9] Figure 2 shows the P53-mediated response to cellular stress signals.

MDM2 Gene

The *MDM2* gene, located on chromosome 12q13-14, was first discovered in 1992 by Oliner et al.[20,21] The protein synthesis process generates a protein composed of 483 amino acids with an estimated molecular weight of 90 kDa. The protein has four regions. Region I binds to the P53 protein and gene promoter. Region II binds to the ribosomal L5 protein and 5sRNA. Region III contains a zinc finger motif, and region IV mediates protein-protein and protein-nucleic acid interactions.[22,23] MDM2 functions as a suppressor for the P53 protein and plays a role in a feedback mechanism to sustain appropriate levels of P53.[22] Figure 3 displays the regulation of P53 by MDM2.

P53 and MDM2 are involved in an autoregulatory feedback loop. MDM2 is expressed when p53 encourages MDM2 production. MDM2 then suppresses p53 function by promoting nuclear export, blocking transcriptional activity, and stimulating p53's destruction in the cytoplasm and nucleus. P53 is activated by a variety of agents that damage DNA or by oncogenes that are dysregulated. When DNA damage occurs, p53 and MDM2 become more phosphorylated, which stops them from interacting and stabilizes p53. Similarly, ARF protein is induced by active oncogenes and sequesters MDM2 within the nucleolus, stopping p53 degradation.

Under normal conditions, MDM2 binds to p53, reducing its transcription activity and targeting it for degradation. MDM2 can also directly remove P53 from

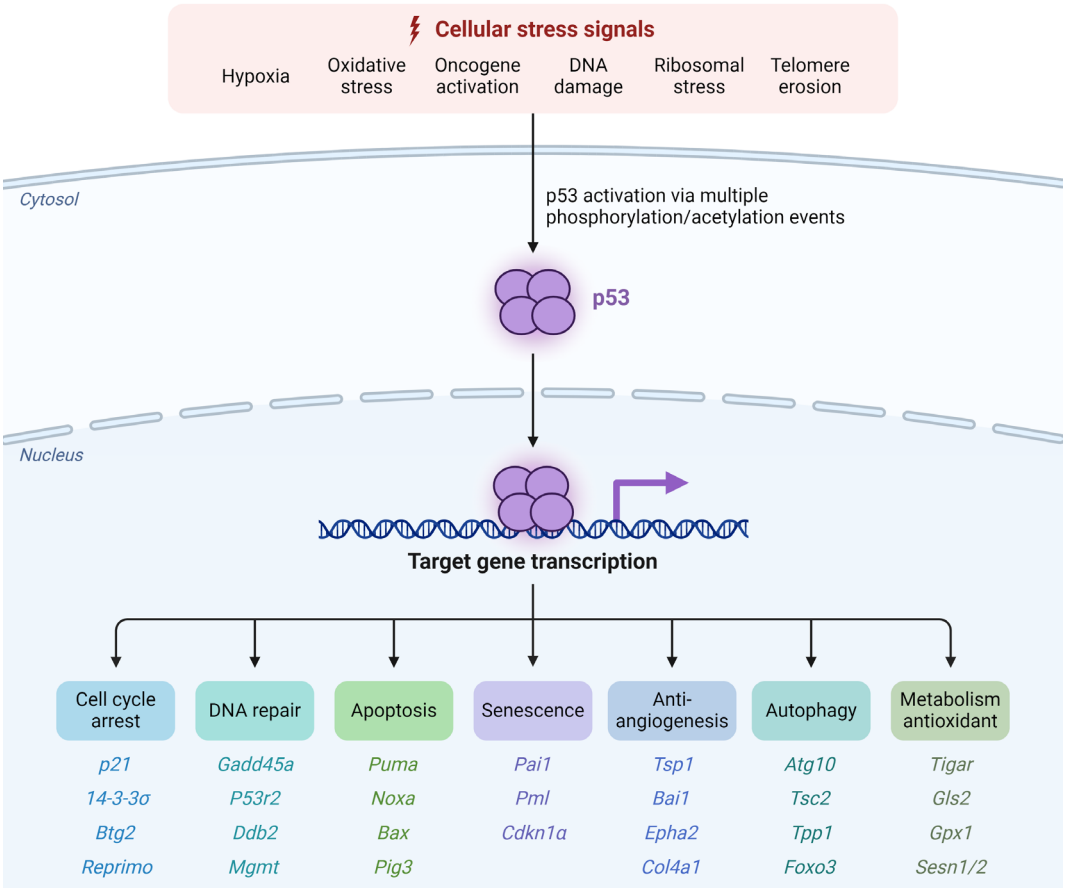

Figure 2. P53-Mediated Response to Cellular Stress Signals. *Source*. Chène.[19] Created with BioRender.com: Confirmation of Publication and Licensing Rights with agreement number: TD26VFYFRL

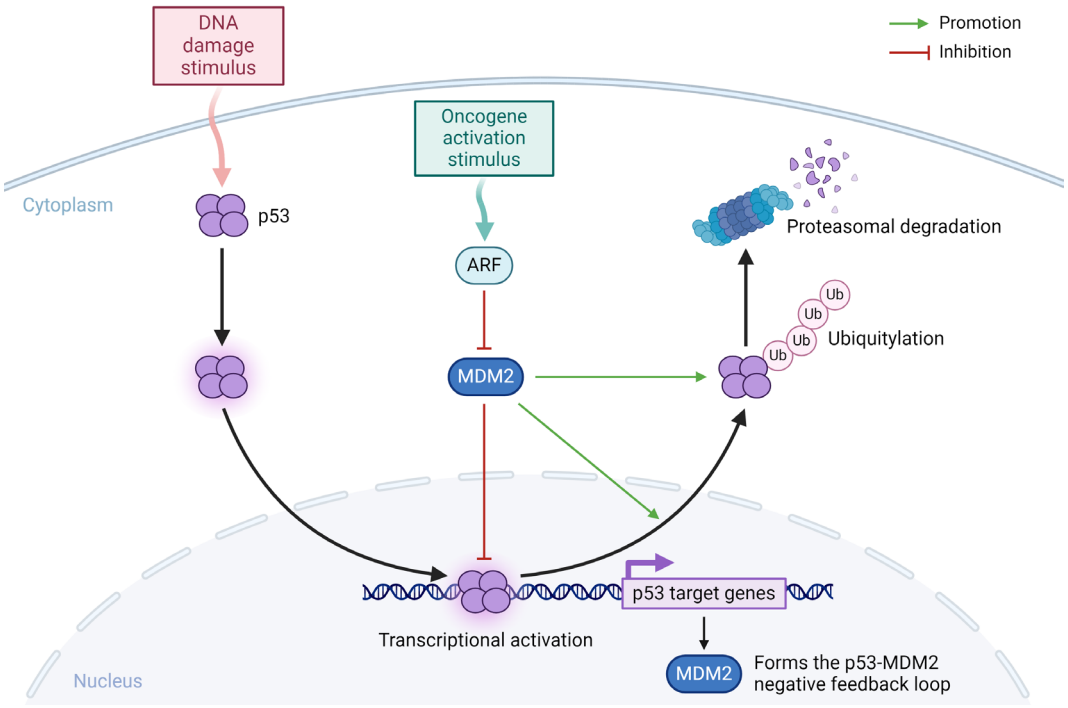

Figure 3. P53 Regulation Via MDM2.[19,24] In an autoregulatory feedback loop, P53 and MDM2 are involved. MDM2 is expressed when p53 encourages MDM2 production. MDM2 then suppresses p53 function by promoting nuclear export, blocking transcriptional activity, and stimulating p53's destruction in the cytoplasm and nucleus. P53 is activated by a variety of agents that damage DNA or by oncogenes that are dysregulated. When DNA damage occurs, p53 and MDM2 become more phosphorylated, which stops them from interacting and stabilizes p53. Similarly, ARF protein is induced by active oncogenes and sequesters MDM2 within the nucleolus, stopping p53 degradation. Created with BioRender.com: Confirmation of Publication and Licensing Rights with agreement number: RP26VFYU9L

cells to decrease its levels.[22] The p21 protein is activated by P53 and plays a crucial role in cell survival. Its expression leads to cell cycle arrest, apoptosis, and increased sensitivity to chemotherapy.[25] MDM2 can also promote the degradation of p21 through proteasome interaction, thus regulating its levels in the cell.[24] MDM2 has been found to play a role in chemotherapeutic resistance in various cancers.[26] It can inhibit apoptosis induced by cisplatin and lead to cisplatin resistance. MDM2 may also contribute to temozolomide resistance by regulating the expression of O6-methylguanine methyltransferase and down-regulating p53. Additionally, MDM2 can induce resistance to doxorubicin by down-regulating wild-type p53 expression. The protein Musashi-2 (MSI-2) has also been found to play a role in chemotherapeutic resistance by enhancing the E3 ligase function of MDM2. Overall, the MDM2-P53 negative feedback loop is associated with resistance to various chemotherapeutic drugs in malignancies.[27] MDM2 can also contribute to chemotherapeutic resistance through a P53-independent pathway by inducing the epithelial-mesenchymal transition process.[27] Overall, the literature review showed the role of MDM2 overexpression associated with radiotherapy in the sensitivity of malignancies, inhibition of apoptosis in tumor cells, promotion of the epithelial–mesenchymal transition process, and elevation of angiogenesis.

MDM4 Gene

Mouse Double Minute 4 (MDM4), also known as MDMX, is a protein that is produced by the *MDM4* gene found on chromosome 1q32.[28] MDM4 belongs to the MDM protein family and is well-recognized as the main inhibitor of P53. It has a substantial influence on the development and advancement of cancer as a factor that promotes its growth. MDM4's N-terminal region forms a binding interaction with P53, which hinders P53's capacity to activate certain genes. The core acidic domain and zinc-finger domain have a role in both the folding and regulation of the protein. The C-terminus of MDM4 has a RING domain that works in conjunction with MDM2 to regulate p53. MDM4 alternative splicing contributes to tumor growth, with MDM4-FL showing greater stability and MDM4-S being widely expressed in tumor cells. Various isoforms of MDM4 may potentially play a role in the development of tumors.[28] MDM4 is important for regulating various life activities controlled by p53.[28] Mutations in the *MDM4* gene can lead to conditions such as dyskeratosis congenita and bone marrow failure.[28] MDM4 has also been found to contribute to tumor progression, with amplifications of the gene associated with higher rates of metastases and a poor response to immunotherapy. MDM4 can also disrupt DNA repair and inhibit the response to DNA damage, leading to genome instability.[29] MDM4 and MDM2 collaborate to suppress P53 expression and activity, whereas MDM4 also enhances the E3 ligase

action of MDM2. MDM4 can also independently regulate other cellular processes, such as lipid storage and estrogen signaling.[28] High levels of MDM4 have been linked to the activation of different oncogenic signaling pathways, including wingless and Int-1, mitogen-activated protein kinase, Janus kinase/signal transducers and activators of transcription, and transforming growth factor β. MDM4 has also been shown to inhibit the function of the tumor suppressor protein FOXO.[30]

CDKN2A Gene

The *CDKN2A* gene, sometimes referred to as *P16*, codes for multiple tumor suppressor 1 (MTS1), which belongs to the INK4 family.[31] The gene is located on chromosome 9p21. It spans 8.5kb and consists of 3 exons. This gene makes a protein with 148 amino acids that may stop the formation of kinase activity complexes by interacting with CDK4 and CDK6, which are connected to cyclin D and CDK4. This compound hinders the process of adding phosphate groups to the RB protein, causing the cell cycle to stop in the G phase.[31] The *CDKN2A* gene has been extensively studied for its role in the p53 signaling pathway. Previous reports demonstrated that the loss of the *CDKN2A* gene in mice led to an increase in tumorigenesis and a reduced lifespan due to the loss of p53 function.[32] Another study showed that mutations in the *CDKN2A* gene were associated with an increased risk of developing melanoma, especially in individuals with a family history of the disease.[33] The *CDKN2A* gene has been associated with other forms of cancer, in addition to its role in melanoma. Research on pancreatic cancer revealed that the prevailing gene alterations were performed in the *CDKN2A* gene and the proto-oncogene Kras. Additionally, it was shown that inhibiting the activation of P16 by Kras was associated with the proliferation of tumors and their spread to other parts of the body.[34] Moreover, a study conducted on individuals diagnosed with lung cancer indicated that those who had mutations in the *CDKN2A* gene exhibited less responsiveness to certain therapies, indicating the gene's significance in the onset and advancement of the illness.[35] Overall, *CDKN2A* is a crucial tumor suppressor gene that has a significant impact on controlling the course of the cell cycle and inhibiting excessive cell proliferation. CDKN2A functions as a safeguard against unregulated cell growth and facilitates the halting of the cell cycle and programmed cell death. CDKN2A, via its products p16INK4a and p14ARF, effectively controls the p53 pathway, guaranteeing appropriate cellular responses to stress and inhibiting the development of tumors. Gaining knowledge about the processes of this gene within the framework of the p53 pathway may provide useful insight into the progression and management of cancer. According to these studies, CDKN2A might serve as a reliable biomarker for predicting cancer patients' survival rates due to its molecular process.

CDKN2B Gene

The *CDKN2B* gene, found on human chromosome 9p21.3, encodes a protein called p15Ink4b, which plays a vital role in regulating the cell cycle by inhibiting the activity of CDK4/6.[36] *In vivo*, *in vitro*, and tumor cohort studies have shown that p15Ink4b is a potent tumor suppressor, and its loss through deletion, mutation, rearrangement, and hypermethylation at 5'-CpG islands is commonly observed in various types of cancer.[36] This gene is also important for the growth and differentiation of dendritic cells, and its loss has been linked to myeloid diseases such as acute myeloid lymphoma and myelodysplastic syndromes.[37] The loss of p15Ink4b does not influence cell proliferation, self-renewal, or apoptosis in myeloid progenitor, but it plays a crucial role in inhibiting aerobic glycolysis, a process often dysregulated in cancer. Overall, p15Ink4b is a crucial component of the p53 signaling pathway, and its loss has been linked to various cancer diseases such as pituitary adenomas, leukemias, lymphomas, cervical cancers, lung and liver cancers, as well as coronary heart disease and type-2 diabetes.[37] The *CDKN2B* and *p53* genes have a strong interaction in the p53 signaling pathway. This interaction is vital for regulating cell growth and division. The findings of a study by Xia et al[36] confirmed that p15Ink4b, the protein encoded by *CDKN2B*, is a more potent tumor suppressor than p16Ink4a, another protein involved in the p53 pathway. p15Ink4b inhibits the activity of CDK4 and CDK6, which are proteins that promote cell cycle progression, while also inhibiting the activity of enolase-1, a glycolytic enzyme often increased in cancer cells. This dual inhibition of cell cycle and aerobic glycolysis makes p15Ink4b a crucial component of the p53 pathway in preventing the formation and progression of cancer.

TP53BP1 Gene

The *TP53BP1*, which is located on human chromosome 15q15-12,[38] encodes the 53BP1 protein. This large scaffolding protein exerts an important role in regulating the response to DNA damage by interacting with modified histones and other effector proteins. The protein contains different regions, including the N-terminal region (1-1,220aa), minimal focus-forming region (1,220-1,711aa), and C-terminal region (1,712-1,972aa), which are important for its function. There are 28 Ser/Thr-Gln sites in the N-terminal region that interact with other proteins. The minimal focus-forming region has two dynein chain domains that help 53BP1 oligomerize and recruit. The C-terminal region also has two BRCA1 carboxyl-terminal domains that interact with p53 and γH2AX, which is important for fixing DNA damage. All these interaction domains of 53BP1 are essential for its role in repairing DNA damage, particularly in heterochromatin, although

their contribution may vary depending on the context of the repair.[38] Eukaryotic cells face numerous threats during DNA replication and cellular metabolism, such as radiation, chemicals, and recombination. Failure to repair DNA damage can lead to cell death or genomic instability, which can result in cancer. DNA double-strand breaks can be fixed in four ways, namely, homologous recombination, non-homologous end joining, alternative end-joining, and single-strand annealing. Homologous recombination and non-homologous end joining are the main pathways used for DNA repair.[38] TP53BP1 regulates the tumor-suppressing functions of p53 by interacting with and stabilizing this protein. This interaction also helps activate the transcription of p53 target genes, which play a crucial role in cell cycle arrest, DNA repair, and apoptosis. TP53BP1 also helps P53 become acetylated, which is needed for it to do its job of activating and stopping tumors. Mutations or dysregulation of TP53BP1 can disrupt this interaction and impair the proper functioning of the p53 pathway, potentially leading to cancer development.[39-41]

Discussion

The tumor, lymph node, and metastasis staging system has witnessed eight changes since its introduction in the 1976 Cancer Staging Manual.[42] These changes are crucial to improving the care of cancer patients. The availability of extensive pathology and molecular data has greatly enhanced our comprehension of cancer biology and clinical characteristics. There is, however, a need for the development of new prognostic methods in the field of cancer that can include an increasing number of prognostic markers.[43] Apoptosis is often characterized by distinct alterations in the structure and metabolic processes that rely on energy.[44] Apoptosis is believed to be necessary for several processes, such as regular cell proliferation, immune system development and function, hormone-driven tissue shrinkage, embryonic growth, and chemically induced cell death. Apoptosis refers to a kind of cell death that is genetically regulated and leads to the targeted elimination of cells.[44] To comprehensively examine the spread, advancement, and spread of cancer, it is essential to consider the processes of apoptosis. The process of cell death consists of three sequential stages (i.e., infusion, determination, and performance). These may arise via either an inherent or external mechanism.[45] P53 is a crucial gene in the process of apoptosis. The p53-induced apoptosis triggers early DNA repair, which may be necessary to reverse cell death. Apoptosis is a regulated and energy-dependent process that initiates a series of cysteine proteases, ultimately resulting in cell death.[44] In my opinion, wherever there is energy, there is also information. DNA energy and genetic information play a critical role in the development and progression of cancer. DNA is the hereditary substance that contains the guidelines for the growth and operation of all living beings. Changes or mutations in DNA can alter the genetic information, which can affect cellular processes and potentially lead to cancer development. Additionally, cancer cells often exhibit high levels of energy consumption, which is necessary for their uncontrolled growth and division. Understanding the relationship between DNA energy, genetic information, and cancer requires important vision into the mechanisms of cancer occurrence and potential treatment strategies.[42] The P53 signaling pathway is an important regulatory mechanism that prevents the development and progression of diseases such as cancer and preserves cellular homeostasis.[44] Apoptosis is regulated by the *P53* pathway.[46] This review study has provided comprehensive insights into the key genes—*TP53*, *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, and *TP53BP1*—associated with the general *P53* signaling pathway. This signaling pathway is a complex network of molecular interactions that regulates DNA repair, apoptosis, senescence, and cell cycle arrest in response to cellular stress. The central element of this pathway is the *TP53* gene, which is responsible for encoding the P53 transcription factor. When activated, P53 performs its cancer-inhibiting role by controlling the transcription of several target genes. Dysregulation or mutations in critical genes in the P53 pathway may result in the loss of its tumor-suppressive functions, which can promote cancer formation. *TP53* is the most well-researched gene in the P53 signaling pathway. Figure 4 depicts targeting therapies for the P53 protein.

This TF operates on several important genes in cell cycle regulation, DNA repair, and apoptosis. TP53 is carefully controlled by translational and post-translational mechanisms to optimize the cellular stress response. MDM2 and MDM4 regulate P53 activity. MDM2 cleaves P53 as an E3 ubiquitin ligase, whereas MDM4 suppresses P53 transcription regulation. Their interaction with TP53 modulates P53 levels and function via a feedback loop. MDM2 and MDM4 disruptions may destabilize P53 and impact carcinogenesis. CDKN2A and CDKN2B inhibit CDKs that regulate the cell cycle. They mostly suppress the cell cycle by inhibiting CDKs. Loss or inactivation of CDKN2A and CDKN2B may impair cell cycle regulation and cause tumors. TP53BP1 responds to and repairs DNA damage. It enhances DNA damage, induced cell cycle arrest, and apoptosis by interacting with p53.[49] *TP53BP1* performs a critical role in preserving the integrity of the genome and inhibiting the buildup of genetic alterations associated with DNA damage.[50] Our previous studies demonstrated that the prevalence of mutations in *TP53*, *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, and *TP53BP1* in cancer may vary depending on the specific cancer type and the population being studied. We analyzed the genetic alterations in the general *P53* signaling pathway-related genes in 10967 samples (10,953 patients) in 32 combined

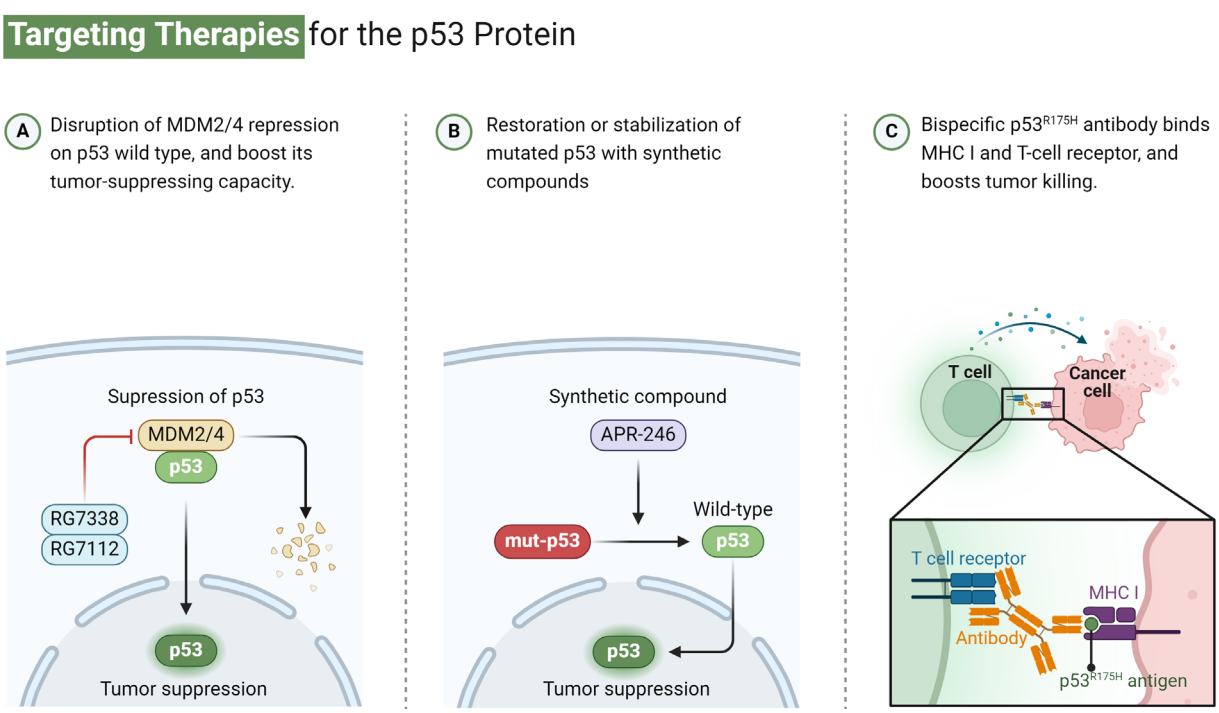

Figure 4. Targeting Therapies for the P53 Protein. *Note*. This figure illustrates different targeted therapy approaches for p53 in cancer.[47,48] Created with BioRender.com: Confirmation of Publication and Licensing Rights with agreement number: XK26VFZ5UV

studies in different cancers (Motalleb, unpublished data). Our results showed that genetic alterations were 36%, 17%, 13%, 3.7%, 3.4%, and 3% for *TP53*, *CDKN2A*, *CDKN2B*, *MDM2*, *MDM4*, and *TP53BP1*, respectively, in all samples of different cancers using bioinformatic methods (Motalleb, unpublished data). In my opinion, the main question is: How can we distinguish between normal and pathological mutations? In other words, we need a new word or term for the true mutation in cancer research. A simple comparison of the frequency of mutations in the six genes in the general p53 signaling pathway in cancer is made as follows:

TP53 mutations are a common genetic anomaly detected in cancer. *TP53* mutations are estimated to occur in almost 50% of all human malignancies, making it one of the most prevalent mutated genes in various types of cancer. Alterations in *MDM2* and *MDM4*, crucial controllers of TP53, are also found in cancer.[50] Mutations in these genes are less frequent than *TP53* mutations. *MDM2* amplification or overexpression is observed in certain tumor forms, including sarcomas and some hematological malignancies. *MDM4* mutations are seldom found but have been recorded in certain disease categories, such as gliomas and breast cancer. *CDKN2A* and *CDKN2B* mutations are associated with the disruption of the cell cycle and could contribute to the development of cancer. The frequency of *CDKN2A* and *CDKN2B* mutations varies depending on the kind of cancer. *CDKN2A* changes, including deletions, mutations, and promoter methylation, are often detected in melanoma, pancreatic cancer, and some types of lung cancer. *CDKN2B* mutations are infrequent but have been observed in a distinct subset of tumors, including gliomas and hematological malignancies. *TP53BP1* alterations have been relatively understudied in comparison to the other specified genes. The documentation of *TP53BP1* alterations in cancer is less comprehensive compared to *TP53* or other genes in the same pathway; however, it has been identified in some forms of cancer. The prevalence of gene alterations may vary depending on the study population, detection procedures, and the specific form of cancer being studied. It is recommended to refer to expert studies and databases for accurate and up-to-date information on the prevalence of gene mutations in different forms of cancer.[50] Clinical trials are currently underway to investigate potential drugs targeting *p53*, *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, and *TP53BP1* in cancer treatment. These targets play vital roles in the development and progression of cancer, and targeting them with specific drugs holds promise for improving cancer therapies.

Targeting *p53*: Adavosertib (AZD1775/MK-1775); this drug is a Wee1 inhibitor that aims to induce synthetic lethality in tumors with P53 deletions or mutations.[51] It has been tested in clinical trials for various cancers, including ovarian cancer, colorectal cancer, and uterine serous carcinoma.[52]

UCN-01: This PKC inhibitor has also shown the ability to induce p53 synthetic lethality. Clinical trials have been conducted for leukemia, lymphoma, melanoma, pancreatic cancer, and other cancers.[53]

Targeting *MDM2* and *MDM4*: Nutlin-3; Nutlin-3 is an

MDM2 inhibitor that disrupts the interaction between MDM2 and P53, leading to P53 activation. It has been investigated in clinical trials for different cancers, including acute myeloid leukemia, solid tumors, and lymphomas.[54]

AMG 232: AMG 232 is another MDM2 inhibitor that has shown promise in preclinical studies. Clinical trials are ongoing to evaluate its efficacy in different types of cancer.[53]

ALRN-6924: ALRN-6924 is a dual inhibitor of MDM2 and MDM4. It is being investigated in clinical trials for solid tumors, lymphomas, and leukemias.[53]

Targeting *CDKN2A* and *CDKN2B*: Palbociclib (PD-0332991); Palbociclib is a CDK4/6 inhibitor that has demonstrated efficacy in combination with other therapies for various cancers, including breast cancer. Clinical trials are ongoing to explore its potential for different cancer types.[53]

Ribociclib (LEE011): Ribociclib is another CDK4/6 inhibitor that has been investigated in clinical trials for breast cancer, neuroblastoma, and other malignancies.[54] Currently, there are no specific drugs that directly target *TP53BP1* in cancer treatment. TP53BP1, also known as a p53-binding protein 1, is a protein that plays a crucial role in the DNA damage response pathway and is involved in the regulation of the tumor suppressor protein p53.[54] However, there are several drugs and therapeutic strategies that indirectly target TP53BP1 or affect its function in cancer treatment. These approaches aim to modulate the *p53* pathway, which is closely interconnected with *TP53BP1*. Here are some strategies that have been explored (Figure 4):

Restoration of wild-type p53 function: Considering that TP53BP1 is involved in the regulation of p53, strategies that restore the function of wild-type p53 can indirectly impact TP53BP1. Various approaches have been investigated, including small molecules that stabilize and reactivate mutant p53, such as PRIMA-1 and PRIMA-1Met.[53]

The inhibition of *MDM2*: MDM2 is a negative regulator of p53 and can lead to its degradation. The inhibition of MDM2 can indirectly affect TP53BP1 by preventing the degradation of p53 and promoting its activation. Several MDM2 inhibitors, such as Nutlin-3 and RG7388, have been developed and tested in preclinical and clinical studies.

Combination therapies: Combining drugs that target different components of the p53 pathway, including TP53BP1, may enhance therapeutic efficacy. For example, combining MDM2 inhibitors with DNA-damaging agents or other targeted therapies has shown promising results in preclinical studies. It is important to note that the development of specific drugs targeting TP53BP1 is an active area of research, and new therapeutic strategies may emerge in the future. Additionally, the use of TP53BP1 as a potential therapeutic target may vary depending on the specific cancer type and the genetic alterations present in the tumor. However, an imatinib positive response in atypical chronic myeloid leukemia was previously reported against TP53BP1.[55]

Conclusion

The general *P53* signaling pathway, which consists of *TP53*, *MDM2*, *MDM4*, *CDKN2A*, *CDKN2B*, and *TP53BP1* genes, is essential for maintaining cellular balance and avoiding the onset of illnesses, namely, cancer. Gaining knowledge about the role and control of these genes is vital for uncovering the molecular processes that cause illness and for creating new treatment approaches that focus on the *P53* pathway. Additional study is required to completely clarify the complex relationships and communication between these genes, with the eventual objective of using this information to enhance diagnostics and focused therapies for different illnesses. It is necessary to distinguish between normal and pathological mutations in the general *P53* signaling pathway. In other words, in my opinion, we have to create and introduce new terms for mutation in molecular cancer research.

Competing Interests

None.

Ethical Approval

Not applicable.

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