Targeting TP53 to Treatment of Cancers: Chance and Challenge

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Abstract. P53 is capable of controlling cell proliferation, senescence and apoptosis, as well as DNA repair through regulation associated genes expression. Nearly 50% of human malignancies harbor mutations in TP53 gene, which were identified as a common feature of many cancers, often leading to the accumulation of abnormal cells and uncontrolled cell growth. Research into therapeutic strategies targeting mutp53 began nearly 20 years ago. However, few drugs have entered clinical trials, and with the exception of China's Gendicine, none have yet been approved for direct patient treatment. With the development of p53-specific targeted therapies and drug delivery systems, targeting P53 to develop effective cancer treatment strategies has been focused on by researchers in recent years. This review mainly summarizes the relationship between P53 and cancer, lists some examples to introduce cancer therapy targeting P53, and analyzes the current chance and challenge of P53 therapy in cancer. The purpose of this paper is to provide new ideas and directions for the research of targeting P53 in cancer.

Keywords: TP53; cancer treatment; p53 pathway; gene mutation.

1. Introduction

TP53, also known as p53 whose discovery dates back to 1979, suppresses tumors through maintaining genome stability [1]. At that time, while studying the SV40 virus's large T-antigen cancer protein, scientists found a protein that interacts with it, which was later identified as TP53. P53 is capable of controlling cell proliferation, senescence and apoptosis, as well as DNA repair through regulation associated genes expression. Nearly 50% of human malignancies harbor mutations in TP53 gene, whereas the remaining tumorigenic cells show a functionally inactive p53 pathway due to various alternative mechanisms although expressing WT p53 protein [2].

In the early stages of research, TP53 mutations were identified as a common feature of many cancers, often leading to the accumulation of abnormal cells and uncontrolled cell growth. TP53 mutations associated with the development of various cancers, displaying particularly high frequency of gene mutations varying between 38% and 50%. In contrast, mutations in TP53 are less frequent in certain other cancers, such as lymphoma, sarcoma, testicular cancer, melanoma, and cervical cancer, affecting around 5% of cases [1].

When mutations occur in TP53, these normal surveillance mechanisms are disrupted, often leading to the accumulation of genetic abnormalities and onset of cancer. TP53 mutations can be classified as either loss-of-function or gain-of-function mutations [2]. Subsequent to the identification of TP53 mutations as a key driver of cancer, efforts were made to search for drugs that could specifically target these mutations. One approach that was to research small molecule inhibitors inhibition of the activity of mutant TP53 proteins. The goal of these inhibitors is to restore the TP53 tumor suppressor function or induce degradation of the mutant protein.

Research into therapeutic strategies targeting mutp53 began nearly 20 years ago. However, few drugs have entered clinical trials, and with the exception of China's Gendicine, none have yet been approved for direct patient treatment. With the development of p53-specific targeted therapies, the small molecules targeting mutp53 have been focus on many years with an optimistic outcome. In addition, the development of drug delivery systems has enabled significant progress in gene therapy, such as inhibiting the degradation of RNAi. Therefore, targeting P53 to develop effective cancer treatment
strategies has been focused on by researchers in recent years. This review mainly summarizes the relationship between P53 and cancer, lists some examples to introduce cancer therapy targeting P53, and analyzes the current chance and challenge of P53 therapy in cancer, providing novel strategies or directions of targeting P53 treatment for cancer.

2. P53 Mutations, Cancer onset and Therapeutic Strategies

2.1. Loss-of-Function Mutations

This kind of mutation in TP53 result in a non-functional TP53 protein, which cannot bind to its target DNA sequence and initiate transcription. These mutations can be caused by single amino acid deletions or substitutions and are relatively common in cancer, which occurs in approximately 50% of cancer patients [2]. The function loss of this gene results in accumulation of genetic abnormalities in the cell, which includes DNA mutations and karyotype evolution, a phenomenon that cells develop abnormal numbers of chromosomes copies, which can accelerate cancer development [1]. Gain-of-function mutations can also arise through TP53 gene amplification or overexpression, then deregulating transcriptional programs and promoting oncogenic signaling. The main goal of targeted TP53 therapy for loss-of-function mutations is to restore TP53’s normal function in safeguarding the genome, including gene therapy and small molecule inhibitors [3]. Gene therapy using wild-type TP53 vectors has shown promise in restoring TP53 function by delivering normal TP53 genes into cancer cells, where they express normal TP53 protein and initiate transcription of its target genes. Additionally, inhibitors of small molecular that specifically bind this mutated protein were developed to recovery wild-type TP53 function by blocking mutated TP53’s interaction with other proteins or modifying TP53’s transcriptional output [3]. In addition, targeted TP53 therapy for gain-of-function mutations aims to overcome these oncogenic activities by interfering with TP53’s interaction with other proteins or modifying TP53’s transcriptional output [4]. One method is the use of allosteric inhibitors that bind to TP53 at sites distinct from its DNA binding domain [3]. These inhibitors are able to interfere with TP53’s ability to bind to its target DNA sequence, block oncogenic signaling pathways, and restore normal TP53 function.

2.2. Gain-of-Function Mutations

This kind of mutations in TP53 result in a range of oncogenic activities that promote tumorigenesis. These mutations can deregulate normally suppressed transcriptional programs and lead to oncogenic signaling activation and tumor suppressors inactivation [3]. Additionally, gain-of-function mutations can alter TP53’s interaction with other proteins, leading to constitutive activation of oncogenic signaling networks and promoting cancer cell growth and survival [3]. Importantly, gain-of-function mutations are more difficult to treat than loss-of-function mutations because they retain TP53’s ability to bind to target DNA sequences, making it more difficult for therapeutic interventions to block TP53’s oncogenic activities. A possible way is p53-specific genetic therapeutics to recover its function have shown promise in cancer treatment [5]. Restoring p53 function has been identified as a critical mechanism for cancer cells to undergo programmed cell death, circumventing resistance to traditional chemotherapy and radiation therapy.

3. Targeted TP53 Therapy in Cancer

Targeted TP53 therapy is a rapidly developing area of cancer research in recent years, with the goal of restoring normal function to the TP53 protein in cancer cells through target mutated TP53 proteins in cancer cells while sparing healthy cells (Table 1). This therapy can improve the outcomes by restoring normal TP53 function and slowing cancer’s development. The process of developing effective TP53-targeted therapies has involved multiple stages of research and development, including the identification of TP53 mutations and their role in disease etiology, the discovery of small molecule inhibitors and other drugs designed to specifically target these mutations, and finally, the evaluation of these drugs in clinical trials.
As gene therapy products targeting P53, they are very effective in treating cancer using gendicine in more than 30,000 patients [4], which induces repairment of DNA and arrest of cell cycle through enhancement of programmed cell death.

An approach for gene therapy is the use of RNAi-based therapies that silence mutated TP53 transcripts, thereby reducing oncogenic activities and slowing cancer development. However, the major challenges of using siRNAs are dramatically degrade by endo/lysosomes before reaching to target genes [6]. An alternative approach involves the use of antisense oligonucleotides (ASOs), a chemically synthesized oligonucleotides for 12-30 nucleotides binding with specific RNA to block the translation of mutant p53 mRNAs, enabling the production of wild-type p53 protein [6]. For example, ASCO1419, an ASO inhibitor of mutant p53 in phase I trials with promising antitumor activity, leading to the inhibition of metastasis and sensitization of tumors to chemotherapy [7]. Another alternative strategy involves the use of gene therapy to deliver wild-type p53 into tumors including viral vectors and plasmid DNA. Delivery of wild-type p53 using adenovirus successfully inhibited tumor growth in animal model of cancers through recovery p53 function. AAV-based vectors show promise for delivering wild-type p53 to solid tumors and offer the potential for systemic administration. For example, Adp53, an adenovirus expressing wild-type p53, has shown promise both efficacy and safety in preclinical studies as a monotherapy for glioblastoma [8].

Additionally, specifically target mutated TP53 proteins using small molecular have been developed to restore wild-type TP53 function by blocking mutated TP53’s interaction with other proteins or modifying TP53’s transcriptional output. One such example is APR-246 TP53 mutations, which has shown optimistic results in hematologic and solid tumors in studies of animal models and patients. APR-246 was discovered using a high-throughput screening approach, in which over 200,000 small molecules were evaluated for their ability to recovery of TP53 function [9]. This screening approach identified a compound termed APR-246, which was able to restore TP53 function and induce apoptosis in cells with mutant TP53, with limited effects on cells with wild-type TP53 [9]. In addition, sotorasib (LCL-161), another small molecule inhibitor of mutant TP53, showed promising antitumor activity in solid tumors patients [10].

Other drugs discovered include peptides and antibodies that specifically bind to mutant TP53 proteins and restore their normal function or induce their degradation, which are in the preclinical and early clinical stages of research and development [1]. One example is a therapeutic antibody termed DS-8201a, which binds to the pSer315 mutant isoform of TP53 and restores its normal function. DS-8201a has shown promise in ovarian cancer xenograft models, which made it enter into treatment of solid tumors patients [11]. Another study shows that p53 seropositive patients with higher level of antibodies are certain HLA-DQ and HLA-DR alleles. For example, in vitro experiments showed that mutant p53 peptides have a 10-fold higher affinity for HLA-DQ7 molecules than wild-type p53 peptides through selecting its matched HLA molecules [12].
**Table 1.** The drugs of targeting P53 treatment of tumors

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drugs</th>
<th>Specific mechanisms</th>
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</thead>
<tbody>
<tr>
<td>RNAi-based therapies</td>
<td>siRANs</td>
<td>Silence mutated TP53 transcripts to reduce oncogenic activities and inhibit cancer development</td>
</tr>
<tr>
<td>Antisense oligonucleotides (ASOs)</td>
<td>ASCO1419</td>
<td>Bind specific RNA to block the translation of mutant p53 mRNAs</td>
</tr>
<tr>
<td>Delivery of WTP53</td>
<td>AAV-based vectors-Adp53</td>
<td>Delivery of wild-type p53 using adenovirus to inhibit tumor growth</td>
</tr>
<tr>
<td>Small molecular inhibitors</td>
<td>APR-246 and sotorasib (LCL-161)</td>
<td>Restore TP53 function and induce apoptosis in cells with mutant TP53</td>
</tr>
<tr>
<td>Antibodies</td>
<td>DS-8201a</td>
<td>Bind to the pSer315 mutant isoform of TP53 to restore its normal function</td>
</tr>
<tr>
<td>Peptides</td>
<td>mutant p53 peptides</td>
<td>Increase affinity for HLA-DQ7 molecules to restart wild-type p53 peptides functions</td>
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4. **Challenge and Prospective**

Despite the promise of p53-specific genetic therapeutics, there are several difficulties that need to be resolved before application in clinic, such as improve efficacy and reduce toxicity, as well as overcome some barriers in terms of cost and ethical concerns.

One major obstacle is the limited delivery efficiency of these agents to solid tumors. Systemic delivery of genetic therapeutics is often hampered by their poor stability and bioavailability, as well as their inability to effectively penetrate tumor tissue [13]. To overcome these limitations, novel delivery systems and conjugation strategies are being developed to improve the biodistribution and tumor targeting of these agents. For example, lipid-based delivery systems and cationic polymers have shown promise for enhancing the delivery of genetic therapeutics to solid tumors, especially for RNAi treatment [6]. Until now, few of therapeutic RNAi have begun to evaluate their efficacy because of instability of naked nucleic acids both outside and inside cells, thus leading to extremely lower bioavailability. Alternatively, nanoparticles are capable of enhancing the uptake and controlling the release speed due to the effects of protecting RNA from degradation [6].

Another challenge is the potential for resistance to p53-specific genetic therapeutics. Tumors can develop resistance through a variety of mechanisms, including further mutations in p53 or activation of parallel signaling pathways that lead to growth and survival independent of p53 status. To address this issue, combination therapy with inhibitors of these resistance mechanisms is being investigated to potentiate the antitumor effects of p53-specific genetic therapeutics. For example, combining Adp53 with inhibitors of kinases upstream of p53 has shown promise for potentiating the antitumor effects of Adp53 in preclinical studies of melanoma and colorectal cancer [8].

Besides efficacy and resistance, the major problem for patients with tumor gene therapy need to be considered cancer recurrence and low survival since many candidates choosing for this kind of treatment are late stage. The severity of cancer affects treatment effectiveness of gene therapy, which genetic spectrum (mutations) and the complexity of the immune system will increase, eventually leading to compared with early malignant tumor patients, the treatment of the subjects were not successful [14]. Therefore, choosing patients with certain stage is important to evaluate optimally these reagents of various TP53-targeted therapies.

5. **Summary**

In conclusion, the future prospects for p53-specific genetic therapeutics are exciting, with several ongoing clinical trials evaluating different approaches for recovery the functions of WTP53 in patients.
of cancers. It is likely that these trials will lead to new treatment options for cancer patients in the future, particularly those with mutations in the p53 gene. However, further research is needed to address the challenges and improve the clinical outcomes associated with these therapies. Questions that need to be addressed include how to optimize delivery systems for systemic administration and how to potentiate the antitumor effects of p53-specific genetic therapeutics through combination therapy with other inhibitors. Additionally, further understanding of the mechanisms of resistance to p53-specific genetic therapeutics is needed to develop strategies to overcome this resistance. The promise of p53-specific genetic therapeutics lies in their ability to recovery its function, leading to tumor growth inhibition and sensitization to chemotherapy agents.

The mutations identification also led to the development of companion diagnostics. These companion diagnostics are becoming increasingly important as personalized medicine gains popularity in cancer treatment. One example is a companion diagnostic test termed IVD-p53Dx, which can identify NSCLC tumors harboring TP53 mutations from other NSCLC tumors without TP53 mutations. This test is used to select patients for evaluating sotorasib as a treatment for NSCLC with TP53 mutations and other therapies targeting TP53 mutations in clinical experiments. The use of companion diagnostics in clinical trials evaluating targeted therapies has enabled more accurate patient selection and monitoring.

References