Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

p53 Correlation with Triple-negative Breast Cancer and Potential Treatments

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Abstract. Triple-negative breast cancer (TNBC) poses significant challenges in the field of oncology due to its prevalence and difficulty in treatment. TP53, which codes for a tumor-suppressing transcription factor p53, is crucial for the prevention of tumor development. When mutated, its role is reversed, as mutp53 provides new oncogenic properties and is correlated with the onset of cancers. Studies have presented a strong correlation between mutp53 and TNBC tumorigenesis by providing metastatic properties, uncontrolled proliferation, and immune evasion properties for the tumor cells. This review comprehensively examines the structural changes in mutp53, how the oncogenic properties are acquired through structural mutation, the cell signaling pathway that mutp53 alters that further leads to cancer development, and the novel treatments of TNBC using PRIMA-1, NVP-BEZ235, and histone deacetylase inhibitors (HDACIs). At last, the advantages of the treatments and challenges they currently are facing are critically evaluated. Further research directions, including examining toxicity and personalized treatments, are proposed for improving clinical outcomes for TNBC patients.

Keywords: p53 mutant; triple-negative breast cancer; cellular signaling; immunotherapy.

1. Introduction

Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the absence of three types of receptors: estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). TNBC accounts for 15-25% of cases among all breast cancers. The distribution of TNBC across all age groups exhibited a comparable pattern. Among different ethnic groups, Hispanic and African American descendants pose a higher risk of getting TNBC. Genetic mutation is a major risk factor for TNBC, and in the human body, genome stability is crucial for sustaining the basics of life [1]. The TP53 gene, which codes for p53 protein, is essential in maintaining such stability. p53 is a tumor-suppressing transcription factor that is involved in multiple cellular processes, including regulating cell cycle arrest from G1 to S phase, regulating DNA Damage Repair (DDR), and inducing programmed apoptosis. TP53 mutation, leading to the production of p53 mutants (mutp53), is highly correlated with the onset of TNBC. It has been recorded that p53 mutation is observed in over 80% of TNBC patients, which draws the attention of extensive research.

Two major types of mutants are present for mutp53: loss of function (LOF) and gain of function (GOF) mutants. LOF mutp53 leads to loss of tumor-suppressing ability, compared to WT p53. In addition to this, GOF mutp53 also acquires new oncogenic properties. These oncogenic properties include promoting cancer cells proliferation, developing metastatic cancer cells, acquiring chemoresistance towards cancer therapies, promoting metabolic reprogramming, etc [2]. Therefore, GOF mutp53 plays an important role in TNBC development, and multiple emerging TNBC treatments are utilizing mutp53 as a target molecule. Mainly three types of treatments are present, which aim to restore WT p53 function, degrade mutp53, or suppress mutp53 transcription. PRIMA-1 and PRIMA-1MET (APR-246) are currently under preclinical trials, which are capable of enhancing the effectiveness of existing TNBC treatments. As the PI3K/mTOR dual inhibitor, NVP-BEZ235 blocks tumor proliferation and promotes the degradation of mutp53. Histone deacetylase inhibitors (HDACIs) offer a new therapeutic approach, by inhibiting mutp53 production at a genetic level [3]. However, the treatment approaches still face tremendous challenges. Although the therapies

target GOF mutp53, the mutants in different patients have varying mutation loci and residues, leading to difficulties in producing the ubiquitous treatment method. The therapies also present cytotoxicity and other side effects for the patient, making the treatment unsafe. Also, the different therapies are shown varying effectiveness on different TNBC tumors, which might require a combination of therapies. Furthermore, the number of clinical trials conducted on these therapies is very limited, which makes it difficult to conclusively determine and comment on the most promising treatment method. Therefore, more future research could be performed in search of a safer and more effective treatment against TNBC by targeting mutp53. T-cell vaccines that induce cytotoxic T-cell responses against mutp53 positive tumor cells are promising, and yield strong immunogenic responses against mutp53 with hotspot mutations. Furthermore, the utilization of artificial intelligence, machine learning, and metadata is increasing for not only tumor diagnosis, but more importantly, for the design of more personalized treatment to tackle variants of mutation.

2. Overview of TNBC

Breast cancer is a disease originating in breast tissues. The cancer cells emerge in breast ducts, leading to ductal carcinoma, or in the lobules, leading to lobular carcinoma. The symptoms of breast cancer at an early stage are mainly lumps and thickening. If left untreated, cancer also has the potential to spread around the body into other tissues through the blood or lymphatic vessels. There are multiple subtypes of breast cancer: Hormone Receptor-Positive Breast Cancer, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer (HER2), and Triple Negative Breast Cancer (TNBC) [1]. According to the WHO, breast cancer is the second most common disease worldwide. In the year 2022, there were 2.3 million women diagnosed with breast cancer and 670000 deaths globally [4]. This has underscored the need to understand the mechanism of cancer development and effective treatments to reduce the global impact of breast cancer.

TNBC as a subtype of breast cancer, is characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) expression [5]. TNBC accounts for approximately 15-25% of total breast cancer cases, and its incidence has shown a steadily increasing trend in recent years. A mix of non-modifiable and modifiable risk factors contribute to the onset of TNBC. Non-modifiable factors include age (more than 80% of incidences in patients above 50 years old), sex (female patients predominate), race and ethnicity (high prevalence among African descent), and genetics (BRCA1/2, TP53 mutations) [6-8]. Modifiable factors refer to lifestyle choices, including consumption of alcohol and tobacco, exposure to carcinogenic chemicals, and BMI [9]. Apart from the risk factors, multiple signaling pathways are altered, leading to tumorigenesis and metastasis for TNBC. The Notch signaling pathway enhances tumor metastasis, the Wnt/β-Catenin pathway enhances motility of tumor cells, the TGF-β signaling pathway promotes migration, and the PI3K/mTOR pathway leads to uncontrolled proliferation [10-13].

This complexity of TNBC makes it the most challenging breast cancer to treat. Current mainstream treatment strategies for TNBC include chemotherapy, radiotherapy, and immunotherapy. However, the effectiveness is limited, and they are faced with multiple challenges. TNBC cells do not possess ER, PR, and HER2, which are typically targeted by therapies in other breast cancer subtypes. TNBC cells are aggressive and highly metastatic and have a high possibility of recurrence. TNBC cells also showed resistance to the therapies. Therefore, a novel TNBC treatment strategy that has the potential to overcome the research barriers are currently in urgent need.

3. p53 Structure and Function

The gene TP53, which codes for p53 tumor-suppressing protein, is involved in multiple important cellular functions. p53 is a tetrameric protein that consists of four functional domains: N-terminal transactivation domain (TAD), DNA-binding domain (DBD), tetramerization domain (TD), and C-terminal regulatory domain (CTD) [14]. The full-length p53 has not been produced with high resolution in experimental settings, and the prediction from AlphaFold provides important insight in

its full structure. TAD is responsible for transcriptional activation of downstream genes with the facilitation of DBD. TD, located around the C-terminus of p53, drives the formation of p53 tetrameric structure, which is crucial for normal function. CTD is the site for post-translational modifications, which regulates the interaction of p53 with other proteins. DBD, as the most important functional domain in p53, is crucial for its ability to act as a transcription factor. DBD ranges from residue around 102-292 and is important in regulating p53 binding affinity to DNA molecules. Utilizing residues including Arg248, Arg273, Arg280, etc., p53 can form direct interaction with the DNA backbone or form hydrogen bonds to interact with nucleotide bases, thus achieving binding to DNA.

The binding of p53 to DNA, thus acting as a transcription factor, is a crucial step in regulating important cellular functions and regulating downstream genes. Activated p53 directly regulates the transcription of over 500 genes, and at the same time, indirectly regulates multiple other genes, achieving regulation on a wide variety of cellular processes. The p53 plays a pivotal role in sensing and responding to DNA damage. When the cell exhibits DNA damage, p53 will activate and upregulate DNA repair genes. For example, p21 transcription and translation will be induced, which further binds to the cyclin-CDK complex, resulting in cell cycle arrest, and preventing damaged DNA from further proliferation. The p53 also induces apoptosis after sensing DNA damage. p53 can induce apoptosis indirectly, through upregulating expression of PUMA and NOXA. It is also capable of directly inducing apoptosis, through the interaction with anti-apoptotic proteins and neutralizing their function [15].

p53 is also an important regulator of immune functions of the cell, mainly through the negative regulation of NF-kB. NF-kB regulates the pro-inflammatory responses by activating the expression of pro-inflammatory cytokines and chemokines. The balance between p53 and NF-kB maintains a stable anti-inflammatory microenvironment [16]. Furthermore, p53 regulation also takes place in the adaptive immune system. T cell recognition of antigens can be promoted by p53 through the upregulating expression of MHC class I molecules in antigen-presenting cells. It could be concluded that multiple functional domains provide vast regulatory functions to p53, especially the DBD, which is crucial for p53's action as a transcription factor. Thus, the structural integrity of the DBD is significant in the normal function of p53.

4. p53 Mutants and Effects

Mutant p53 (mutp53) plays a critical role in cancer development by disrupting the normal functions of wild-type p53. There are two main types of mutp53: Loss of Function (LOF) and Gain of Function (GOF) mutants. In LOF mutants, p53 loses tumor-suppressing functions, including DNA repair and apoptosis induction. In GOF mutants, besides the function loss, there are additional oncogenic properties, including promoting tumor progression, metastasis, and drug resistance. According to the IARC TP53 database, in the screening of GOF mutation frequency in tumor cells, mainly the residues in the DBD are affected, having a significantly higher mutation frequency than other functional domains [17]. This draws the attention of further investigation. The most frequent mutations in DBD are R175H, R248Q, and R273H, each contributing to the increasing of risk of cancer development.

R175H, a mutation that affects residue 175, changes normal arginine (CGC) to histidine (CAC). This mutation has a significance of clonal origin: this missense mutation is detected in a wide range of the same tumor tissue, which suggests that it originates from a progenitor cell and affects tissue through clonal expansion. R175H affects the DNA binding ability of mutp53, altering the tumor-suppressing ability. Also, in tumor tissues, loss of heterozygosity is observed for this mutation. This indicates that tumor cells with R175H mutation will be selected and reinforce its tumorigenesis property. R248Q is another hotspot GOF mutation of mutp53 and has significant effects. In wtp53, as mentioned before, R248 directly interacts with the DNA backbone and achieves DNA binding. This R248Q mutation changes the structural and chemical identity of wtp53, shifting a positively charged, relatively large arginine residue into an uncharged and smaller glutamine residue, which disrupts binding to target DNA sequences. This mutation also enables mutp53 to directly bind to various transcription factors that it does not normally bind to, including NF-Y, ETS, p63, and p73, which further induces to

abnormal proliferation, cell invasion, tumor survival, and metastasis [18]. The R273H mutation affects p53 function in similar mechanisms. Additionally, it alters the control of p53 on Snail protein through ubiquitination and degradation. Snail protein is a key modulator of epithelial-to-mesenchymal transition, which is a crucial process for tumor invasion. R273H disables the degradation of Snail protein, thus leading to its persistence and accumulation, and providing metastatic potential for tumor cells [19].

Another important characteristic of mutp53 is its stability under proteolytic degradation. Wtp53 will be degraded through ubiquitination mediated by MDM2. However, in mutp53, as structural alteration occurs through mutant residues, this proteolysis process is disrupted, leading to the persistence of mutp53 in the cell and its constant tumorigenesis action. This property of mutp53 reduces the effect of radiotherapy and chemotherapy. The mechanism of cancer elimination of these therapies is to induce DNA damage thus cell death through the intrinsic apoptosis pathway of cancer cells. However, as mutp53 persists in cancer cells, the intrinsic apoptosis pathway is blocked, leading to therapy resistance [20]. Overall, the findings have presented the multifaceted role of mutp53 in the disruption of normal cellular pathways and tumor development in general. This provides a consolidated foundation for the further examination of its detailed role in TNBC development.

5. The Role of GOF mutp53 on TNBC Development

The GOF mutp53 disrupts a network of transcription control, leading to uncontrolled proliferation and metastasis, immune evasion, and stemness of TNBC cells. Mutp53 leads to the development of uncontrolled proliferation and metastasis for TNBC cells. This is achieved mainly through influencing the Epidermal Growth Factor Receptor (EGFR). EGFRs are a type of receptor tyrosine kinase, often phosphorylated, and serve as a binding site for various signaling molecules. When EGFR is bound by signaling molecules, they will be internalized into endosomes, and recycling is needed. Mutp53 enhances the rate of EGFR recycling, which promotes the constant activation of downstream signaling pathways, such as the PI3K/AKT pathway [21]. This further leads to a higher production of cyclins, which drives the cell cycle progression, accelerating cell division rate and ultimately leading to uncontrolled proliferation. The pathway will also increase growth factor production level, which is observed in breast cancer patients. Furthermore, mutp53 inhibits an anti-metastatic protein, p63. This inhibition leads to loss of control on downstream migration genes, contributing to the metastatic property of TNBC cells.

Immune evasion refers to the process by which cancer cells avoid detection and elimination by the host's immune system. Immune evasion is common and significant in TNBC, which leads to rapid progression of disease, poor prognosis, and recurrence of cancer. Multiple pathways contribute to immune evasion driven by mutp53. First, a proinflammatory microenvironment is created through the mutp53 action on NF-kB. Through promoting NF-kB production, a higher level of proinflammatory cytokine and chemokine production will be induced, creating a tumor-promoting microenvironment. In TNBC, over-expression of CXCL10, CX3CL1, and LTB chemokines is observed, which promotes cell migration activity in the tumor-promoting microenvironment [16]. Secondly, mutp53 affects MHC molecule production. As mentioned before, wtp53 upregulates the expression of MHC class I molecules, which enhances the recognition of tumor cells by cytotoxic T cells. For mutp53, this effect is reversed and MHC class I molecule expression is inhibited, and the ability of immune cells to present antigen is limited, facilitating the evasion of cancer cells from the adaptive immune system [22]. Thirdly, mutp53 manipulates immune checkpoint molecules, diminishing immune cell responses. Mutp53 downregulates the production of microRNA miR-34a. Normally, the miR-34a level is higher and suppresses PD-L1 expression. When its level is reduced by mutp53, PD-L1 expression is enhanced and more PD-L1 molecules will be presented on the tumor cell surface. When tumor cells interact with T cells, PD-L1 binds to the receptor on activated T cells, which confers an inhibitory signal. Therefore, T cell activity will be dampened. Even if cytotoxic T cells are presented with tumor-specific antigens, their action will be diminished. Such overexpression of the PD-L1 molecule is observed in TNBC patients, contributing to immune evasion [23].

Cancer stem cells (CSC) are a minor population within the cancer cells that has the capacity for self-renewal and promotes tumor development and metastasis. In TNBC development, CSC contributes to the aggressiveness of the disease. In normal conditions, wtp53 is involved in the regulation of self-renewal and differentiation of stem cells, providing a balance through homeostasis. Contrastingly, mutp53 mainly confers stem cell properties for the tumor cells, leading to the development of CSC. In previous in vitro investigations on hematopoietic and mesenchymal stem cells, the R248Q mutation of mutp53 improves the survival and replication of the cells, and the same mutation contributes to the development of malignancy in patients. Mutp53 also disrupts the epigenetic modifications on histone proteins and contributes to the development of CSC. H3K27me3 modification is applied to the histone proteins, leading to a more condensed chromosome structure and silencing the genes promoting differentiation. In TNBC development, mutp53 interacts with the catalytic subunit EZH2 of Polycomb Repressive Complex 2 (PRC2), which enhances the deposition of inhibitory modification on histone proteins. The persistence of such inhibitory modification will prevent the activation of lineage-specific gene transcription and thus maintaining the stemness in CSCs [24].

6. Targeting p53 Mutant for TNBC Treatment

Novel TNBC treatment approaches that target mutp53 can be classified into 3 main categories: mutp53 reactivation, degradation, and transcriptional suppression. The study conducted by Synnott et al. presents a treatment strategy for TNBC through the reactivation of mutp53, converting it into a form with wtp53 properties. PRIMA-1 and PRIMA-1MET (a derivative form) are small molecule compounds that are designed to specifically target cancer cells with mutp53. The mechanism of function restoration of mutp53 is achieved by the binding between PRIMA-1 and mutp53. PRIMA-1 will bind to the cysteine residues within the DBD of mutp53 covalently, and induce a structural change for mutp53. This structural change will reestablish its correctly folded structure. Although this is not a complete restoration of the structure, this structural change is sufficient for mutp53 to bind to its regular binding partners and sustain its tumor-suppressive properties. This study presents the ability of PRIMA-1 to restore wtp53 function in over 20 breast cancer cell lines, highlighting its broad range of action [3]. The challenges of PRIMA-1 in TNBC treatment is mainly in the complexity when treating with other cytotoxic compounds. The efficacy of this combined treatment varies between different cell lines, which indicates that specific modification in the treatment is needed when applying on different patients. The study presented by Cai et al. discusses another different approach, promoting the degradation of mutp53 in tumor cells through the PI3K/mTOR dual inhibitor NVP-BEZ235. BEZ235E acts as a small-molecule drug and disrupts the PI3K/AKT/mTOR pathway, which is crucial for cell growth and proliferation. BEZ235 will suppress the signaling pathway action and inhibit its downstream transcription factors, such as p70S6K. This could limit the uncontrolled proliferation in TNBC cells. A surprising finding in the paper suggests that the degradation of mutp53 driven by BEZ235 is independent of the ubiquitination-proteolysis pathway and the autophagy pathway [25]. As mutp53 has stability under ubiquitination and proteolysis this strategy is promising as it bypasses the barriers set by mutp53.

The research conducted by Wang et al. explored the use of histone deacetylase inhibitors (HDACI) to reduce mutp53 transcription while preserving wtp53 transcription [26]. Histone deacetylase removes acetyl groups from histone proteins and plays an essential role in gene expression regulation by changing chromosome structure. HDAC inhibitors such as suberoyl anilide hydroxamic acid (SAHA) and sodium butyrate (NaB) function by causing hyperacetylation in their target proteins. The study shows how HDACIs inhibit TNBC cell proliferation by downregulating mutant p53 mRNA levels through its interaction with YY1. YY1 is a transcription factor that binds to the region between -102 and -96 of the p53 promotor and enhances its transcription. HDACIs have been shown to hyperacetylate YY1 at residue 170-220, which alters its DNA binding ability. This reduction in DNA binding, therefore, leads to a reduction in mutp53 mRNA production and reduced proliferation of cancer cells in TNBC. This treatment approach presents a specificity towards mutp53, as it

specifically downregulates mutp53 level without affecting normal wtp53 action. However, multiple challenges are presented for HDACIs. The potential off-target effects of SAHA and NaB were not evaluated in the study, and the broad-range activity of HDACIs on both histone and non-histone proteins could present potential toxicity to the patient. Also, as this is an in vitro preclinical study, transferring the findings into a clinical setting is time and resource-consuming.

7. Challenges and Future Research

Considering the complexity of the correlation between mutp53 and TNBC, there are multiple challenges faced by both conventional and novel treatments targeting mutp53.

First, tumor heterogenicity presents in TNBC patients. Although mutp53 is highly prevalent in TNBC patients, it is not an entirely ubiquitous target. Even if the patient acquires mutp53, the type of mutation and the locus of mutant residue differ. Also, the tumorigenicity of some tumor subpopulations may not be entirely due to the effect of mutp53. Other gene mutations, such as BRCA1, BRCA2, GATA3, etc., could be the source of tumor development [27]. Therefore, it is extremely challenging to use a single treatment method to resolve this complex problem. For future research efforts, a screening program should be designed for analysis of the type of biomarkers that the patient acquires and thus presents the most suitable treatment strategy for the patient.

Secondly, treatment resistance will emerge. In traditional treatments such as chemotherapy and radiotherapy, TNBC patients with mutp53 show resistance, as these treatments induce apoptosis through an intrinsic pathway, which is suppressed by mutp53. This resistance is overcome by the novel strategy mechanistically, as the strategy aims to degrade or suppress mutp53 production.

Thirdly, the toxicity of treatments has not been validated in clinical trial stages. The novel strategy utilizes members of cellular signaling pathways that are also crucial for the function of normal cells. For PRIMA, it will be converted into an electrophile when enters the cell and has the potential to bind to cysteine on other cellular proteins. Similarly, for BEZ235E and HDACIs, their target on PI3K/mTOR signaling pathway and YYI transcription factor might affect the cell division, progression of cell cycle, and proliferation in normal cell. For future research efforts, the in vitro studies should be upscaled into animal experiments on humanized mice or further developed into clinical trials to assess for off-target effect and toxicity.

The novel strategies have overcome some research and treatment barriers, but their limitation and current preclinical status have shown that future research is needed to resolve the above aspects to develop a well-rounded treatment strategy. Future studies should focus on toxicity monitor and reduction, the development of a proper drug delivery system to deliver the drug specifically to the tumor cells, and a screening program to match the biomarker of the patient to the treatment strategies. Overall, optimism should still be given to the novel strategies due to their promising results in preclinical stages.

8. Conclusion

TNBC is still a challenging disease in the field of oncology due to its aggressive nature, high prevalence, and difficulty in treatment. Due to the lack of estrogen, progesterone, and HER2 receptors, conventional treatments that have a consolidated foundation could not be applied to TNBC patients. Therefore, the development of novel treatments for TNBC is an urgent need, and mutp53 could be an ideal target. Mutp53, especially the GOF mutant, disabled its normal tumor-suppressing function while at the same time providing new oncogenic properties for the protein, including metastasis, uncontrolled proliferation, immune evasion, etc. The strong correlation between mutp53 and the development of TNBC tumor cells draws attention and is being examined as an ideal target for treatment. In the current field, treatment strategies using mutp53 as a target aim to reactivate, degrade, or suppress mutp53 using PRIMA-1, NVP-BEZ235, and HDACIs. While each has unique advantages, the challenges are common in the treatments: the need for upscaling from preclinical to clinical stages, the unexamined toxicity of treatment, and the non-ubiquitous efficacy across all TNBC cases. Efforts

and resources should be devoted to upscaling current strategies and to the development of early screening programs to provide specific strategies for patients with different biomarkers. Overall, the challenges for TNBC treatment are still present, but optimism should be given to the novel treatment strategies, which could guide us into the future of TNBC eradication.

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