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Targeting P53 Gene in Breast Cancer

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Abstract

Infectious diseases and breast cancer rely heavily on p53, a tumor suppressor that protects genetic integrity. It is present on chromosome 17p13 and controls angiogenesis, programmed cell death, and cell proliferation. The expression of p53 and its isoforms is more predictive of treatment outcomes and responses to chemotherapy for breast cancer patients than the presence or absence of TP53 mutations. Subtype-dependent mutations of p53's negative regulator MDM2 can both be signs of p53 deactivation in breast cancer. Targeting both wild-type and p53 mutant across various subtypes of breast cancer is one possible treatment strategy. Notably, through paracrine signaling, mutant p53 in stromal fibroblasts speeds up the formation of breast tumors. In the progression and trajectory of breast cancer, the pivotal involvement of the p53 gene, alongside the bcl-2 proto-oncogene, is noteworthy. Addressing the role of p53 is crucial in the context of breast cancer development and its course.

Keywords: *p53- MDM2 -MDM4- APR-246- COTI-2-Brast Cancer- IGF-1/mTOR*

Introduction:

In cases of breast cancer, p53 gene mutations are prevalent, occurring in approximately 30% of instances, and are associated with an unfavorable prognosis [1]. The focus of this review paper revolves around the intricate exploration of strategies aimed at targeting the p53 gene in the context of breast cancer [2]. Recognized as a crucial tumor suppressor gene, p53 performs a pivotal role in retaining genomic stability and orchestrating cellular responses to stress. The prevalence of p53 mutations, approximately 30% in breast cancer cases, underscores its significance in disease etiology. Dysregulation of the p53 gene is associated with poor prognoses, emphasizing the urgent need for innovative therapeutic interventions. This paper delves into the multifaceted landscape of breast cancer, shedding light on the molecular intricacies surrounding p53 [3].

Breast cancer patients harboring p53 gene mutations often exhibit compromised DNA repair. The inhibition of poly (ADP-ribose) polymerase (PARP) emerges as a promising avenue to augment treatment responses in breast cancer cells with mutations of p53 [4]. Combinations of nucleotide analogues with PARP inhibitors demonstrate enhanced efficacy in preclinical models, showcasing their potential as a strategic approach against p53 mutant breast cancer. Additionally, the connection between the expression of the p53 gene and clinicopathological features in breast cancer, including factors like tumor grade, size, age, lymph node metastasis, and estrogen receptor (ER) status, highlights the complex role of p53 in the progression of the disease [5].

As researchers delve into therapeutic strategies for breast cancer, p53 mutant and wild type gene become subjects of exploration [6]. Diverse approaches, ranging from small molecule inhibitors to peptides and genetic-based interventions, are actively being investigated [7]. Biochemical modifications of p53 play pivotal roles in regulating its functions [8]. Understanding the nuances of these modifications is crucial for devising

targeted therapies. The flexibility of the p53 network, with its engagement in DNA repair, cell cycle regulation, apoptosis, and senescence, further accentuates its potential as a therapeutic focal point [9]. The objective of this review is to resolve the complexities surrounding the p53 gene, providing valuable insights into the growth of targeted and effective therapeutic interventions [10]. The development of targeted therapies against mutant p53 is an active area of research and may have clinical relevance in treating cancer patients with mutant p53 and it is promising approach due to its crucial role as a suppressor gene of tumor [11].

Structure, Isoforms and Action of p53

p53 is made up of four identical copies of the full-length monomer and has a homotetrameric structure. In order for the tetramer structure to develop, the p53 tetramerization domains are essential [12]. The p53 tetramer is a hollow, skewed cube with two sizes of node-like vertices. The bigger nodes house the p53's central core domains, while the smaller N/C nodes link the monomers together to create dimers, which in turn form the tetramer [13]. The resolution of the p53 core domain, which spans amino acids from residues 96 to 289, has been established using crystallography [14]. The full p53 tetramer's 3D structure offers a thorough representation of p53 architecture and opens the door to a deeper understanding of this essential tumor suppressor protein. It is congruent with biochemical and physiological data currently available [15]. Because of its unique architecture, p53 may bind DNA target sequences that are spaced differently, which is crucial to its ability to transactivate genes and operate as a tumor suppressor. Understanding p53's regulation and how tumor-associated mutations affect its function have both benefited from knowledge of the protein's structural details [15].

The 3D structure of p53 has an impact on how it can control gene expression through different ways. The first is that particular p53 isoforms might modify p53-induced apoptosis and cell-cycle arrest [16]. Furthermore, post-translational changes like phosphorylation, acetylation, and methylation regulate how well p53 binds to DNA recognition regions and interacts with transcription cofactors [17]. Thirdly, p53 collaborates with co-activators and co-repressors as well as other elements of the transcriptional machinery to either activate or repress the transcription of certain genes that are targeted [18]. Major Histocompatibility Complex I expression on cell surfaces is also regulated by p53, and this function is crucial for immune monitoring of cancer and infection [19]. These findings demonstrate the nuanced control of p53 and the way in which it may influence gene expression in a selective manner.

There are several isoforms of the p53 protein, each of which functions differently in the cell. These isoforms result from alternate splicing, alternate translation initiation, and alternate promoter use. The isoform p53/47 lacks the first 40 codons and is associated with endoplasmic reticulum stress and a particular G2 arrest [20]. Another variant, 133p53, which is implicated in regulating cellular senescence [21] and133 amino acids are lacking. The isoform p53, which has a different C-terminus, is also connected to regulating cellular senescence [22]. Additionally, the isoforms 40p53 and 133p53 interact with p53 and have antagonistic effects [23]. Some p53 isoforms behave in a dominant-negative way, impairing the ability of full-length p53 to function [24]. Although the specific roles of p53 isoforms are yet unknown, it is known that they play a role in several biological activities such as DNA repair and gene expression regulation.

Normal tissues express p53 isoforms, which are implicated in various biological activities including apoptosis, tissue regeneration, cell cycle arrest and carcinogenesis. It has been shown that the p53 isoforms express unusually in a range of human cancers, underscoring the significance of these proteins in the initiation and progression of cancer. It is critical to comprehend the many p53 isoforms in order to enhance cancer treatment and forecast clinical outcomes [25]. p53 isoforms have various functions. In addition to affecting macrophage activity and immune cell recruitment, p53 isoforms can control innate and adaptive immune responses. Cancer, early aging, neurological illnesses, inflammation, abnormalities of the embryo, and flaws in tissue regeneration can all result from the expression of various p53 isoforms being out of balance. The shorter p53A isoform in Drosophila melanogaster is the main modulator of pro-apoptotic gene transcription and apoptosis following DNA damage [26]. The p53 isoforms assist the cell in differentiating between various stressors and triggering the appropriate response. The cellular response to therapy can be managed by regulating the expression of p53 isoforms [27].

p53 is a gene that suppresses tumors in addition to being a transcription factor that identifies specific sequences. When p53 accumulates in response to cellular stress signals, it sets off the antineoplastic reactions of cell cycle arrest, DNA repair, and death [28]. Both internal and extrinsic apoptotic pathways have the ability to induce apoptosis when p53 activates certain apoptotic target genes [29]. In certain situations, p53 may also promote apoptosis through a transcription-independent mechanism [30]. Furthermore, it has been found that p53 regulates translation by drastically lowering translation initiation, suggesting that control over translational activity is another way that p53 inhibits growth [31].

p53 is necessary for controlling the activity of cancer cells. Cellular reactions are caused by p53 in response to numerous stimuli including DNA damage, oncogene activation, and oxidative stress. Additionally, it controls processes including fatty acid, mitochondrial respiration, glycolysis, amino acid, and autophagy as well as other aspects of energy metabolism. Additionally, p53 mutations may lead to the emergence of new oncogenic activities that affect cellular metabolism and promote the growth of tumors. P53 is a critical player in both cancer and metabolic diseases due to its multifunctionality, notably in intracellular metabolisms [32-34].

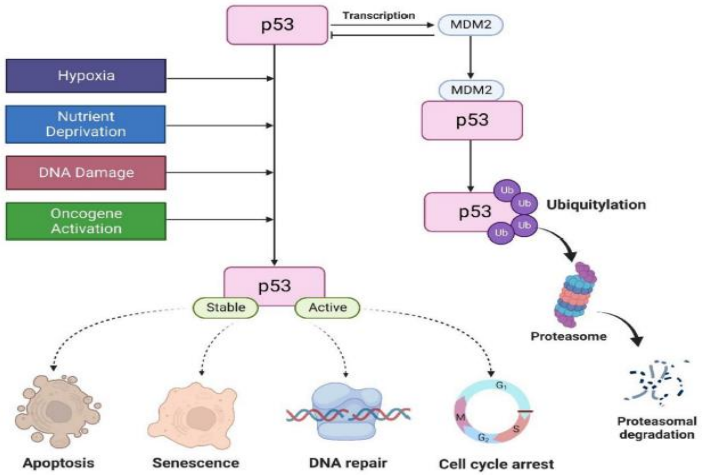
Biochemical modifications of p53

The p53 gene is a linchpin in cellular homeostasis as well as in tumor suppression and undergoes intricate biochemical modifications that intricately regulate its functions. These modifications, encompassing phosphorylation, acetylation, methylation, ubiquitination, and sumoylation, contribute to the dynamic orchestration of p53's diverse roles in cellular processes. Phosphorylation, a pivotal modification, influences p53's stability, DNA binding activity, and interactions with proteins implicated in cell cycle regulation and apoptosis [35]. Acetylation, another critical modification, enhances transcriptional activity of p53, fostering cell cycle arrest and apoptosis [36]. Methylation, on the other hand, can modulate p53's DNA binding ability and transcriptional activity, adding another layer of complexity to its regulatory network [37]. Ubiquitination marks p53 for proteasomal degradation, leading to a reduction in its protein levels [37, 38]. Sumoylation, the attachment of small ubiquitin-like modifiers, regulates p53's subcellular localization and transcriptional activity [39]. This intricate web of modifications highlights the nuanced and multifaceted nature of p53's regulatory mechanisms, unveiling potential avenues for targeted interventions.

In the realm of breast cancer research, understanding the implications of these biochemical modifications on p53's functionality is imperative. For instance, phosphorylation of p53 has been linked to its pivotal role in orchestrating DNA repair mechanisms and influencing cellular responses to genotoxic stress. Acetylation of p53, enhancing its transcriptional activity, may play a crucial role in dictating cell fate decisions, especially in the context of breast cancer progression [39]. Methylation, influencing p53's DNA binding and transcriptional activity, may have implications for the dysregulation observed in breast cancer cases with mutated p53. Ubiquitination and sumoylation, by modulating p53's stability and subcellular localization, respectively, offer potential insights into the molecular intricacies underlying breast cancer pathogenesis [40]. By elucidating the impact of these biochemical modifications on p53 in breast cancer, researchers can pave the way for targeted therapeutic strategies aimed at restoring or modulating p53 functionality to impede cancer progression.

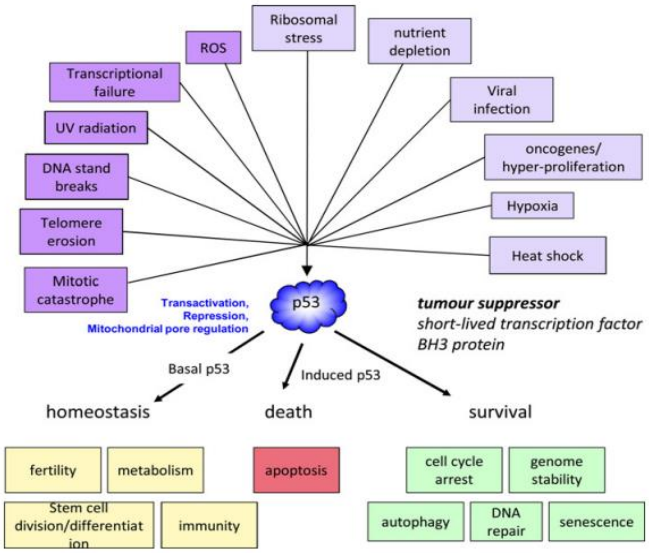
P53 Regulates a Wide and Flexible Genome Network

Found in both the nucleus and the cytoplasm, p53 serves as a master regulatory transcription factor which preferentially binds to DNA and regulates a vast array of genome networks [41]. The intricate regulatory role of the p53 gene extends across a broad and adaptable genome network in the context of breast cancer [42]. P53 orchestrates a comprehensive and flexible network, modulating various aspects of genetic activity to influence the disease's dynamics (Fig. 1) [43, 44]. This expansive regulatory reach emphasizes the nuanced and pivotal function that p53 plays in shaping the genomic landscape associated with breast cancer [45]. Understanding the wide-reaching impact of p53 regulation provides valuable insights into potential therapeutic avenues for targeting this gene in the context of breast cancer treatment [46].



"Figure (1) Under normal conditions: MDM2 regulates p53 protein. P53 is activated by hypoxia, activation of oncogenes, DNA damage, and nutrient deprivation to regulate cell cycle, apoptosis, DNA repair, and senescence [44]."

The primary attention on p53 for many years has been on its function as a cancer tumor suppressor, garnering its nickname "Guardian of the genome". p53 regulates wide cellular processes by overseeing several cellular activities simultaneously in a specific environment [47]. It controls a variety of cellular functions and promotes DNA repair, controls cell metabolism, prevents angiogenesis, and initiates cell senescence [48, 49]. Through transcription-dependent and transcription-independent pathways, p53 also affects metabolism and intracellular redox homeostasis. Additionally, it has been proven that p53 controls stem cell proliferation and differentiation. It may also serve to shorten lifespans and speed up the aging process, p53 also performs a crucial protective function in fostering skin pigmentation [50]. Coordinating the physiological response to stress and influencing cell destiny is the interaction between p53 and the antioxidant enzyme in the mitochondria (Fig. 2) [51].'



"Figure (2) Stress stimuli that lead to p53 induction: A diverse array of cellular stressors triggers the activation of p53, initiating orchestrated modifications in gene expression and diverse biological responses. The outcomes vary based on the cell type and the nature, intensity, and duration of the initiating stress. Stress events leading to p53 induction through DNA damage response pathways are emphasized on the left in a shade of lilac. Some biological processes may undergo regulation in a homeostatic fashion, modulated by basal or low levels of p53. Reactive oxygen species are abbreviated as ROS [51]."

It is now established that p53 is essential for controlling metabolism. By regulating genes involved in intermediate metabolism and mitochondrial respiration, p53 can increase mitochondrial activity and decrease flow via the pentose phosphate and glycolytic pathways. Consequently, p53 may prefer mitochondrial oxidative phosphorylation as the primary ATP generation pathway and decrease the production of substrates necessary for cell division and development. The p53-dependent control of these genes also prevents the Warburg effect [52], which happens when oncogenic activities increase aerobic glycolysis and flow via the pentose phosphate pathway. Moreover, the pathways that govern proliferation, survival, and energy consumption are influenced by the IGF-1/mTOR (mammalian target of rapamycin) pathways, which are under the direction of p53 [53]. The intricate relationship between cell lineage, activation triggers, and the foundation of p53's diverse spectrum of functions is its capacity to control different combinations of its numerous target genes (Fig. 3) [54]. Research indicates that overexpression of pro-apoptotic Bcl-2 proteins or p21 may be associated with cell cycle arrest or apoptosis, respectively. However, this obscures the fact that there are numerous other potential outcome modifiers that are part of the overall transcriptional response to p53 activation. Genes have traditionally been considered p53 targets if it connects to the locus and the mRNA is activated. The improved specificity of Global Run-On Sequencing has recently allowed for the detection of nascent transcripts. The features of the p53 targets identified by this investigation provide compelling evidence that non-canonical functions like metabolism, autophagy, tissue remodeling [55].

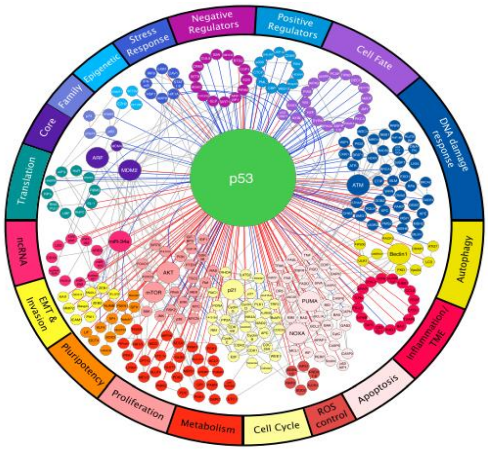


Figure (3) "**The p53 Network:** It exhibits a diverse array of regulators influencing its top-level activity, subsequently overseeing a myriad of distinct biological processes. In this representation, each gene is denoted as a node, and interactions are depicted by lines. Direct p53 inputs are illustrated with blue lines, while direct p53 outputs are represented by red lines. Notably, p53 orchestrates effector processes by activating numerous target genes, forming a complex web of interconnected downstream pathways (gray lines). Interactions are denoted as positive (arrow), negative (T-bar), or modifying (solid circle) [54]."

There has never been a universally successful method of identifying p53 target genes. Just 60 genes were identified as frequent targets in meta-analyses of 16 genome-wide datasets [56]. It is interesting that both surveys focused on a small number of unique cell types and used diverse techniques to induce p53. The transcription of qualitatively varied genes sets, rather than merely variable amounts of the same set of genes, is induced by the cellular environment and a variety of stimuli, according to a key finding. Expecting the same p53 transcriptional response in response to oncogene activation across various tissues seems naïve [57].

The Diversity of TP53 Mutational Events

Exploring the diversity of TP53 mutational events within the context of breast cancer unveils a complex landscape that significantly contributes to the heterogeneity of the disease. The TP53 gene, a main player in maintaining genomic stability, experiences various mutational events, each bearing distinct implications for disease progression. These mutations can manifest as missense mutations, resulting in an amino acid substitution and often leading to the production of a dysfunctional p53 protein. Additionally, frameshift mutations may occur, causing a reading frame shift and the production of a truncated and non-functional protein. Insertions, deletions, and splice-site mutations further add to the intricate tapestry of TP53 mutations, each presenting unique challenges and opportunities for therapeutic intervention [58].

Furthermore, the diversity of TP53 mutational events extends beyond the structural alterations in the gene itself. It encompasses variations in the types of mutations, such as gain-of-function (GOF) mutations, which confer novel oncogenic properties to the p53 protein [59]. This diversity underscores the need for personalized approaches in breast cancer treatment, considering the distinct functional consequences associated with different TP53 mutations. Understanding this diversity is paramount for devising targeted therapeutic strategies tailored to the specific mutational landscape of individual breast cancer cases [60]. The intricate interplay between the diversity of TP53 mutational events and the clinical outcomes in breast cancer patients forms a critical area of investigation, paving the way for more nuanced and effective approaches in the realm of personalized medicine for breast cancer treatment [61].

Hereditary breast cancer and p53

Breast cancer is a distinct disorder made up of various biological subgroups with distinct traits and therapeutic responses. Hereditary breast cancer develops and spreads by the p53 mutations. Mutations in the genes essential for cell proliferation, DNA maintenance, and tumor suppression result in hereditary breast cancer. These mutations can raise the chance of developing breast and ovarian cancer. The most often implicated genes in breast cancer risk syndromes are TP53, PTEN, CDH1, STK11, and NF1[62].

The main genetic abnormalities discovered in Li-Fraumeni Syndrome (LFS) are TP53 mutations, which are present in almost all malignancies, including breast cancer [1]. In particular, in the triple-negative subtype, somatic TP53 mutations are frequent in sporadic breast tumors [44]. Given the high incidence of breast cancer among women with hereditary TP53 mutations, the breast epithelium appears to be particularly susceptible to variations in p53 function [63]. Mutations in TP53, specifically missense mutations affecting codons R175,

G245, R248, and R273, are associated with dominant-negative effects and diminished functionality of the p53 pathway. Missense mutations represent the predominant type of TP53 alteration, accounting for 70% to 80% of cases where a single amino acid substitution results in the production of a defective protein [64]. While these missense mutations can occur throughout the entire p53 molecule, they are predominantly concentrated in the DNA binding domain (80%–90%) [65].

TP53 stands out as the most mutated gene in about 30% of reported breast cancer cases, with the DNA binding domain serving as a hotspot for missense point mutations that impede transcriptional activity. These alterations exhibit a strong correlation with tumor subtypes, particularly influencing the prognosis for breast cancer patients. Breast tumors, classified into luminal-like, basal-like, normal-like, and HER-2 positive subtypes, display varying prevalence of p53 mutations. Major p53 mutations are shown by basal like tumors [66-68]. The presence of p53 mutations, especially in conjunction with HER2 overexpression, significantly worsens prognosis, with inflammatory breast cancer displaying a greater prevalence of p53 mutations than non-inflammatory counterparts. Studies reveal that metastatic breast cancers, regardless of subtype, exhibit poorer overall survival rates in the presence of p53 mutations, particularly in high-grade and advanced-stage cases, and those associated with aggressive subtypes [69-71].

Furthermore, mutant p53 exerts a significant influence on breast cancer development and progression [72]. Mutant p53 triggers the transcription of genes coupled with cell proliferation and interacts with proteins like sterol regulatory element-binding protein to activate the mevalonate pathway [73]. This mutant form further enhances tumor aggressivity and metastatic potential through various mechanisms, including stabilizing the protein through Hsp90 production by Rab coupling proteins, promoting cancer cell invasion and metastasis [74]. Additionally, mutant p53 interacts with adenosine A2b receptor (ADORA2B) and G-protein coupled receptor (GPCR), intensifying invasion and metastasis in breast cancer patients and leading to poorer clinical outcomes [75]. These findings emphasize the intricate function of TP53 mutations in shaping the molecular landscape of breast cancer and highlight their implications for disease progression and patient outcomes [76].

Function of Mutant p53

Exploring the intricate landscape of breast cancer, this review delves into the pivotal role of the p53 gene, unraveling its multifaceted functions in the context of the disease. A significant facet of this investigation involves an in-depth analysis of the function of mutant p53, shedding light on its intricate mechanisms and contributions to the pathological processes within breast cancer. Mutant p53, arising from genetic alterations, showcases distinct behaviors that deviate from the normative functions of the wild-type counterpart. Its aberrant functions extend beyond the canonical tumor suppressor role of p53, encompassing diverse interactions with cellular pathways. The dysfunctional p53 variants exert influences on key cellular processes, thereby sculpting a unique molecular landscape within breast cancer cells [77]. Unraveling the nuances of mutant p53 function becomes paramount in understanding the complexities of disease progression, offering potential insights into targeted therapeutic interventions [78].

Moreover, the review scrutinizes the implications of mutant p53 on clinicopathological characteristics in breast cancer [79]. It navigates through the intricate correlations between the expression patterns of mutant p53 and crucial clinical parameters, including tumor grade, size, patient age, lymph node metastasis, and estrogen receptor (ER) status [80]. This exploration underscores the nuanced involvement of mutant p53 in shaping the disease's clinical manifestations, providing a comprehensive perspective on its impact throughout the continuum of breast cancer progression [81]. In essence, the examination of the function of mutant p53 within the breast cancer milieu unravels a tapestry of complexities, opening avenues for potential targeted strategies and therapeutic interventions in the pursuit of enhanced clinical outcomes [82].

Targeting Mutant p53 Regulated Pathways

Delving into the realm of breast cancer therapeutics, an essential facet revolves around targeting pathways regulated by mutant p53 [83]. The p53 protein, often mutated in breast cancer cases, exhibits gain-of-function activities which can contribute significantly to tumor progression and resistance to therapies. Disrupting the oncogenic functions associated with mutant p53 presents a viable strategy in impeding breast cancer advancement. One approach involves inhibiting the interactors or pathways intricately linked to the GOF activities of mutant p53. By strategically disrupting these associations, researchers aim to curtail the enhanced tumor-promoting effects exhibited by mutant p53, potentially sensitizing breast cancer cells to conventional therapeutic interventions [84].

Beyond inhibitory strategies, alternative approaches focus on reactivating or restoring the function of mutant p53 to its wild-type counterpart. This endeavor seeks to mitigate the detrimental effects of mutant p53, rendering it more akin to its normal, tumor-suppressive form [85]. Strategies such as inducing synthetic lethality, promoting degradation, and employing gene therapies that introduce the wild type p53 gene into tumor cells are being explored [86]. This multifaceted approach towards mutant p53-regulated pathways in breast cancer reflects the dynamic landscape of therapeutic research, aiming to unravel innovative strategies for more effective and targeted interventions in the complex milieu of breast cancer biology (Fig. 4) [35].

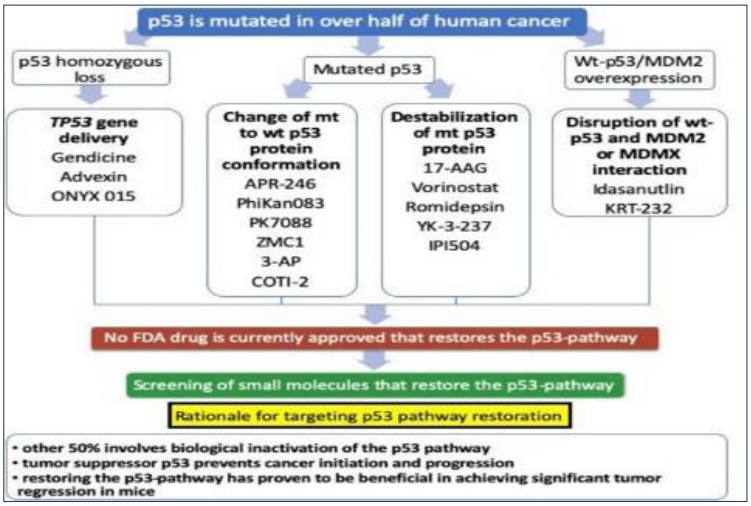


Figure (4): Therapeutic approaches via targeting Mutant p53 Regulated Pathways [35].

Targeting p53 for Cancer Treatment

The endeavor to target the p53 gene for cancer treatment stands at the forefront of innovative therapeutic strategies. As p53 constitutes a vital guardian of genomic stability, aberrations in its functionality, particularly in the context of cancer, prompt the exploration of targeted interventions. A significant aspect of targeting p53 involves the inhibition of "poly (ADP-ribose) polymerase", an approach that has shown promise in enhancing treatment responses, especially in cancer cells carrying p53 mutations. This strategy emerges as a dynamic avenue, potentially sensitizing cancer cells to therapeutic interventions [87]. Combinatorial approaches, integrating nucleotide analogues with PARP inhibitors, present an intriguing prospect, showcasing enhanced efficacy in preclinical models of p53 mutant cancers [88-90]. By understanding the intricate molecular landscape surrounding p53, researchers aim to unravel novel therapeutic modalities that can selectively and effectively target cancer cells, providing a nuanced and tailored approach to treatment.

The exploration of targeting the p53 gene in cancer treatment extends beyond conventional methods, encompassing a diverse array of approaches such as small molecule inhibitors, peptides, and genetic-based interventions [91]. Biochemical modifications of p53 provide potential targets for therapeutic intervention [92]. Each of these modifications plays a distinct role in regulating p53's functions, offering unique opportunities for modulating its activity [93-95]. The inherent flexibility of the p53 network, which governs essential cellular processes and underscores its potential as a versatile therapeutic target [96, 97]. This comprehensive exploration aims to pave the way for novel and effective strategies in cancer treatment, leveraging the intricate regulatory mechanisms of the p53 gene to develop tailored and precise interventions for improved clinical outcomes.

The common mutations and downregulation of p53, which are present in the majority of human malignancies, are among its therapeutic limitations. Amyloid aggregates are formed when the p53 protein is mutated because it is prone to unfolding and aggregating [98]. P53 aggregation results in loss of DNA binding with transcriptional activity which is linked to cancer grading. Moreover, the tumor-inhibitory action of mutant p53 is compromised due to its altered metabolic regulatory roles in comparison to the wild-type protein. It is yet unknown whether drugs that target malfunctioning p53 are clinically effective, despite efforts to create methods to restore normal p53 expression and activity [99]. Although p53 lacks enzymatic activity, low molecular weight catalytic inhibitors cannot block it, unlike numerous cancer-driver oncoproteins that have been effectively targeted for cancer therapy. Additionally, the majority of p53's subcellular location is nuclear, meaning that high molecular weight medications like monoclonal antibodies cannot access this site. Indeed, targeting nuclear proteins for cancer therapy has proven challenging, with the exception of ligand-activated transcription factors like the androgen and estrogen receptors. It was therefore necessary to adopt fresh

perspectives and a distinct methodology for creating medications that target mutant p53 as opposed to the conventional method of creating treatments that target cancer driver genes. It's long been known that a large number of missense mutations affecting mutant p53 change the protein's structure and cause it to unfold [100]. Recent articles indicate that, the most ongoing therapeutic trials targeting p53 in cancer are still at a preliminary stage, only three compounds have made it to phase III clinical trials, the mutant p53-reactivating medication APR-246, the MDM2 antagonist and COTI-2. Thus, it will be very early to conclude whether p53 targeting will be successful in the treatment of cancer or not. Most of the p53-targeting investigations for cancer therapy up to this time involved medications that either activate mutant p53 or prevent wild-type p53 from degrading [101].

p53 Alterations and Response to Therapy

In various human malignancies, it is hypothesized that the absence of functional p53 plays a fundamental role in indicating the cancer's resistance to radioactivity and chemotherapy. This concept finds substantial backing from investigations involving cell death in mice with p53 knockouts, as well as observed associations between the therapeutic response of human tumors in vivo and the p53 status determined through immunochemistry or single-strand conformational polymorphism (SSCP) analysis [102]. Essentially, p53 could increase chemosensitivity by inducing apoptosis through transcription-independent pathways, in addition to transcriptionally activating proapoptotic genes like bax and repressing antiapoptotic genes like bcl-2. The CD95/CD95 ligand system-mediated drug-induced suicide pathway may also be p53-controlled [80].

However, by stimulating DNA repair, p21-mediated and p21-independent growth arrest, and differentiation, as well as by amplifying the transcription of antiapoptotic genes like bcl-x, p53 may reduce chemosensitivity. Research on cell cultures suggests that the cellular environment plays a major role in determining how changing the p53 state affects chemosensitivity [103]. In otherwise healthy, non-cancerous cells, p53 dysfunction may increase rather than decrease chemosensitivity. Targeted disruption of the p53 gene, however, causes increased sensitivity to radiation, as opposed to lower susceptibility, in certain cell types derived from p53-knockout animals. With rare exceptions, transformed cells that have maintained p53 function typically develop chemoresistance when p53 function is inhibited [80].

Tumour cells may therefore be given chemoresistence by preexisting molecular changes or by a subsequent accumulation of molecular abnormalities following p53 loss, as opposed to p53 activity loss alone [83]. At last, noteworthy patterns of p53-mediated modulation of chemosensitivity that are specific to tumour cell types and drugs are starting to surface. Growth arrest is frequently caused by p53 gene transfer into tumour cells, although this can also make the cells more resistant to most chemotherapeutic medications [104].

Drugs in Clinical Trials Aimed at Reviving Mutated p53

Eprenetapopt/APR-246:

Eprenetapopt, formerly recognized as APR-246, stands out as the most extensively investigated medication for reactivating mutant p53. Given the thorough discussion of its mechanism of action elsewhere, this overview will provide a concise summary [91]. Eprenetapopt first changes into MQ, which then attaches to certain thiol groups in the p53 DNA-binding domain to enhance its anti-cancer effect. The changed thiol residues of MQ differ based on the presence or absence of DNA binding in p53. After MQ binds, the mutant p53 restructures to take on the structure of the wild type. It can regain its wild-type functions thanks to this transition, such as causing apoptosis and preventing the growth of cancer cells. [105].

The possible toxicity of eprenetapopt was examined considering multiple preclinical trials that showed its anti-cancer effectiveness. In overall assessment, eprenetapopt demonstrated general tolerability. The detection of cell cycle halt, initiation of apoptosis, and elevated expression of p53 target genes in the cancerous cells of several treated subjects provided evidence supporting the reactivation of mutant p53 [106].

COTI-2:

Third-generation thiosemicarbazone medication COTI-2 is said to have a wide range of anti-cancer properties [107]. COTI-2 inhibits mTOR signalling and activates AMP-activated protein kinase (AMPK). Given that wild-type p53 has been demonstrated to simultaneously activate AMPK and inhibit mTOR, these effects could be the result of p53's reactivation to its wild-type counterpart [108]. The anti-cancer potential of the medication may be further enhanced by these COTI-2 actions. In fact, mTOR inhibition by medications like everolimus is a tried-and-true method of treating some malignancies [109].

In a phase I clinical trial (NCT02433626), COTI-2 has been evaluated as a monotherapy or in conjunction with established medicines for the treatment of several types of recurring malignancies. Numerous clinical studies indicate that COTI-2 is tolerated well, and the most common side effects were abdominal pain along with uneasiness, vomiting, and weariness. Only 2 (8%) out of 24 patients received treatment that required a drop in amount of COTI2 that was given. There don't seem to be any published data on tumour regression in COTI-2-treated patients as of yet [91].

Arsenic Trioxide:

In the pursuit of targeting the p53 gene in breast cancer, Arsenic trioxide (ATO) emerges as a noteworthy contender. Traditionally utilized for treating acute promyelocytic leukemia, ATO exhibits the capability to revive p53 mutant variants distinguished by structural modifications. This reactivation proves effective in impeding tumor cell growth and reinstating normal functionality, both in vivo and in vitro [110]. Unlike eprenetapopt, ATO exhibits a distinctive mode of action, not activating the mutant of p53 with contact mutations or initiating the transcription of target genes of p53 harbors such mutations. The exploration of ATO's potential in reactivating mutant p53 in breast cancer aligns with the overarching theme of targeting the p53 gene, offering a unique avenue for therapeutic investigation and underscoring the diverse strategies being explored within this research domain [111].

Furthermore, it has been documented that the mutant protein is degraded by ATO, a reactivating p53. Therefore, it seems that ATO can counteract the actions that promote cancer through two distinct methods [110]. The well-established pharmacological and toxicological features of ATO may provide it with an advantage over another mutant p53-reactivating medications like eprenetapopt and COTI-2 [112]. Therefore, it should be a great fit for being repurposed to treat different tumour types, particularly those with structural p53 alterations. In fact, a phase I trial called PANDAtrial recently started evaluating ATO's effectiveness, safety, and acceptability in patients with ovarian and endometrial malignancies who were resistant and had structural p53 alterations [85].

PC14586:

Unlike the previously discussed medications that revive p53 mutations, PC14586 selectively reactivates p53 proteins that have the Y220C mutation. The p53 protein develops a tiny pocket as a result of this mutation, which makes it unstable to heat and unable to connect to DNA, as was previously discussed in this article. However, only about 2% of all tumours in humans have this mutation, making it comparatively uncommon among malignancies [113].

Exploring innovative strategies to target the p53 gene in breast cancer, the focus on the Y220C mutation presents a unique avenue for evaluating potential low molecular weight inhibitors tailored to the mutant p53. Notably, the compound PC14586 has demonstrated its efficacy in reactivating and stabilizing the p53 Y220C mutant protein within cells harboring this mutation. This intervention results in cell cycle arrest along with the transcriptional activation of key genes associated with wild-type p53 [114]. The current progression of a phase I/II clinical trial is dedicated to investigating the pharmacodynamics, safety, pharmacokinetics, and potential efficacy of PC14586 monotherapy in patients who have advanced solid tumors with p53 Y220C mutation. Encouragingly, initial findings shared at the American Society of Clinical Oncology meeting underscore the generally well-tolerated nature of PC14586, with 79% of treated patients experiencing grade I/II side events (Fig. 5) [91]. This ongoing research endeavors to pave the way for the advancement of targeted therapeutic approaches in breast cancer, specifically tailored to address distinct p53 mutations, holding significant promise for future clinical applications.

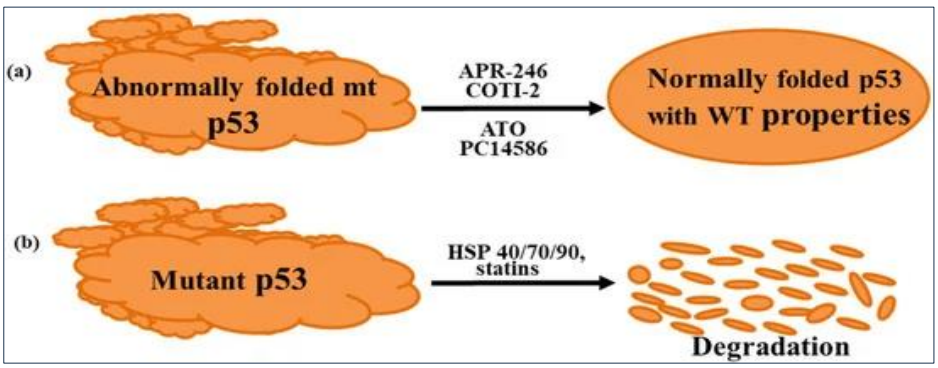


Figure (5): "Strategies used to target mutant p53. (a) Reactivation of mutant p53 to a form with wild-type properties, (b) degradation and elimination of mutant p53. ATO, arsenic trioxide; HSP, heat shock protein [91]."

Mutant p53 and Cancer Immunotherapy:

Immune Recognition of p53 in Cancers:

Several genes are implicated in the immunological response to cancer and are regulated by p53. Immune cells like natural killer T cells, macrophages, T-cells, NK cells and dendritic cells, act as main sources of expression for the p53 target gene TRAIL (Fig. 6) [115]. TRAIL represents an attractive candidate for synergy with immunotherapy due to its ability to engage the p53 target gene DR5, inducing apoptosis selectively in various cancer types [116]. Given the advanced development of TRAIL drugs and agonists targeting DR5 for clinical applications across diverse cancer types, exploring this cytokine as a potential p53 target holds considerable promise in eliciting both an immune response and apoptosis. However, further investigation into the pathways of non-canonical TRAIL and effects of potential immunosuppressive associated with TRAIL administration is crucial before progressing to clinical translation [117].

The primary role in activating the innate immune response lies with TLR3, 5, 7, 8, and 9. These receptors also stimulate the synthesis of type I interferon through IFN regulatory factors. Additionally, p53 can directly activate IRF5 and IRF9. IRF5 plays a role in inducing cancer cell death and initiating the transcription of pro-inflammatory cytokines. Curiously, IRF9 is believed to support p53-mediated IFN upregulation in response to viruses, but it may also increase IL6 production and STAT3 activation, which could aid in the survival of cancer cells [118].

Numerous distinct cell types express the Fas receptor, a death receptor and p53 target that, when bound by a ligand, causes apoptosis. Analyzing mice with mutations in the Fas or FasL genes for lymphoproliferation (lpr) and generalized lymphoproliferative disease (gld), respectively, showed that abnormalities in the Fas receptor result in an increase of CD4−CD8− T-cells, autoantibody production, and loss of immunological tolerance. Taken together, these data imply that T-cell activation-induced cell death is mediated by Fas and FasL expression and also they play a vital role in development of T-cell [119].

p53 and the Immune Response:

Numerous investigations have revealed that p53 has the ability to modify the number of cells and their level of activation in the tumor microenvironment (TME). By inducing cell demise and/or nullifying the immunosuppressive capacity of myeloid-derived suppressor cells (MDSCs), triggering the unmutated form of p53 has the potential to remedy an immunosuppressed tumor microenvironment (TME). Additionally, p53 activation has the capability to enhance the expression of the NK cell ligand ULBP2 on malignant cells, thereby amplifying the anti-tumor efficacy of natural killer (NK) cells [117].

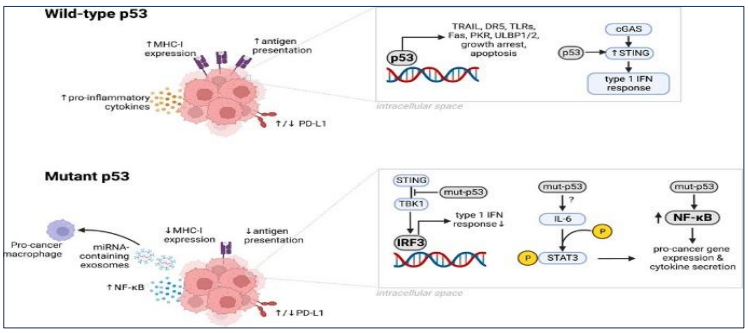


Figure (6): Mutant p53 with microenvironment of tumors [115]."

To enhance the transportation of MHC class I and the expression of MHC-peptide complexes on tumor cells, p53 can activate TAP1. Moreover, p53 collaborates with IFN-γ to initiate the MHC class I pathway. In cells lacking p53, these effects mediated by TAP1 and IFN-γ are nullified. Another study suggests that p53 boosts MHC class I production by elevating the levels of the enzyme endoplasmic reticulum aminopeptidase 1 (ERAP1). It is crucial to validate the in vivo functional significance of these p53-dependent impacts on the activation of cytotoxic T-cells and tumor regression [120]."

p53 Antibodies as Diagnostic Marker for Cancer:

The investigation into the therapeutic potential of targeting the p53 gene in breast cancer has unveiled a promising avenue with the exploration of p53 antibodies as diagnostic markers for cancer. In recent years, these antibodies have emerged as valuable tools in the realm of cancer diagnostics, showcasing their efficacy in detecting and characterizing p53 protein expression. The intricate interplay between p53 gene alterations and cancer pathogenesis underscores the significance of developing reliable diagnostic markers to enhance early detection and prognosis assessment. Pioneering studies have demonstrated the utility of p53 antibodies in accurately identifying aberrations in p53 expression, thereby aiding in the stratification of breast cancer cases based on distinct clinicopathological characteristics [121]. Moreover, the specificity and sensitivity of p53 antibodies contribute to their potential application in differentiating breast cancer subtypes and predicting therapeutic responses. The integration of p53 antibodies into diagnostic protocols holds promise for refining personalized treatment strategies, facilitating timely interventions, and improving overall patient outcomes [117].

As researchers delve deeper into the multifaceted landscape of p53 in breast cancer, the utilization of p53 antibodies as diagnostic markers represents a critical advancement in the field. The nuanced understanding of the p53 pathway and its intricate involvement in cancer progression necessitates sophisticated diagnostic tools, and p53 antibodies prove to be instrumental in meeting this demand. This paradigm shifts in cancer diagnostics, fueled by advancements in antibody-based technologies, not only augments the precision of diagnostic assessments but also paves the way for a more comprehensive comprehension of the molecular intricacies governing breast cancer. The exploration of p53 antibodies as diagnostic markers stands as a testament to the ongoing efforts in harnessing innovative strategies to unravel the complexities of breast cancer, fostering a future where early detection and targeted interventions converge for enhanced patient care [122].

Extending this research to a broader range of cancer types holds promise for the development of p53 vaccines transferring wild-type p53 to immune cells and chimeric antigen receptor (CAR)-T cell therapy. Such investigations also shed light on the administration of p53 activators, considering potential unexpected effects on immune cells [123].

Conclusion:

The P53 gene in breast cancer is a promising target for the development of more specialized and powerful therapies. p53 gene mutations are frequently observed in breast cancer patients, and this gene is essential for controlling cell proliferation and limiting the formation of malignancies. By specifically targeting the P53 gene, researchers and clinicians may be able to develop therapies that can directly address the underlying genetic causes of breast cancer, leading to more personalized and effective treatment options for patients. Additionally, immunotherapy has demonstrated promise in directing the body's immune system toward the destruction of cancerous cells. Further research and clinical trials are required to fully investigate the possibility of targeting the P53 gene in breast cancer, preliminary results are encouraging and call for more research into this strategy.

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