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Exploring the Significance of p53 Gene in Lung Cancer: Etiological Factors, Clinical Implications, and Therapeutic Approaches

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Lung cancer is a type of cancer that originates in the lungs, which are responsible for breathing. The p53 gene plays a critical crucial role in inhibiting cancer progression by regulating cell growth, DNA repair, and apoptosis. In lung cancer, p53 mutations are common and associated with aggressive tumor growth, chemotherapy resistance, and poor survival outcomes. This article reviews explores the etiological factors and therapeutic approaches related to p53 dysregulation in lung cancer. Early detection is key for improving treatment response success and patient survival. Research on p53 mutations in lung cancer has provided valuable insights into the molecular mechanisms driving tumorigenesis and treatment response. Targeted therapies for the treatment of lung cancer treatment have shown immense potential by targeting the p53 pathway. It is critical to understand the clinical significance of p53 mutations as they play a crucial role in determining the success of treatment and the patient's prognosis. Personalized treatment approaches must be considered, and future research should focus on developing new targeted therapies, expanding knowledge of p53 mutations in other cancer types, and improving diagnostic tools for to identifying p53 mutations in lung cancer patients. By investing in these areas, we can pave the way for more effective and personalized treatment for lung cancer patients.

INTRODUCTION

Lung Cancer and the Significance of p53 Gene

Lung cancer originates in the lungs, the organs responsible for respiration [1, 2]. It typically begins when abnormal cells in the lung tissue grow out of control in the lung tissue, and forming a tumor [3]. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two primary kinds types of lung cancer. It has been observed that NSCLC is the most expected kind type of lung cancer, accounting for approximately making up about 85% of all cases based on statistical data [4]. SCLC is less common frequently occurring, but it is more aggressive [5]. While it is widely accepted that smoking is the cause of reason of for lung cancer, it's it is important essential to recognize acknowledge that other factors, such as like radon, asbestos, and air pollution, can also increase boost the risk of developing acquiring this disease this illness [6]. Symptoms of lung cancer include a cough, chest discomfort, difficulty breathing, fatigue, and sudden weight loss. The appropriate treatment depends therapy choices depend on the stage and type of the disease nature of the illness [3]. This may can include surgery, chemotherapy, radiation therapy, targeted treatments tailored to aspects of tumor biology, and immunotherapy to boost the body's body's response. Early detection is extremely important essential to improve in improving the chances of survival for individuals dealing with lung cancer [7]. The p53 gene is widely recognized as a player in the prevention preventing the progression of cancer progression, serving as a tumor growth suppressor gene it serves as a gene that suppresses tumor growth [8]. In the field of lung cancer, it has been discovered that mutations in the p53 gene have been found to be common, affecting occur frequently, affecting a proportion- up to fifty percent- of all cases [9]. The importance of studying the complexities of the p53 gene within in the context of lung cancer lies in its association with increased cell growth, resistance, to chemotherapy, and, unfortunately, reduced chances of overall survival overall [10]. Through research into the role of the p53 gene in regulating cell growth, DNA repair, and apoptosis, scientists have gained valuable insights into how the irregular functioning of this gene may can contribute to the development and spread of lung cancer. Extensive research on the p53 gene has contributed significantly to our understanding comprehension of the intricate molecular mechanisms that govern the growth and spread of lung cancer. By studying the function of the p53 gene, researchers can identify potential targets for new therapies and develop personalized treatment strategies based on an individual patient's patient's genetic profile [11]. In addition, the p53 gene is a promising biomarker for predicting prognosis and response to therapy in individuals diagnosed with lung cancer. Studies have shown that patients with non-mutated p53 respond better to chemotherapy and have a longer overall survival rate than those with mutated p53 [12]. Therefore, the study of studying the p53 gene in lung cancer is essential for advancing our understanding of this disease and developing effective treatments for patients.

The P53 Gene and Its Role in Lung Cancer

The p53 gene is a key crucial tumor suppressor gene that plays recreates an essential function in stopping the evolution of cancer. Acting as a guardian of the genome, it regulates the cell cycle, repairs damaged DNA, and promotes apoptosis (programmed cell death) in cells that cannot be repaired. In normal cells, the p53 gene is tightly regulated and kept in check by a complex complicated network of signaling pathways paths [9]. Within In the realm of lung cancer, aberrations within the p53 gene interfere with obstruct its normal function typical functionality thereby permitting cells to uncontrollably proliferate and multiple, allowing thereby permitting cells to proliferate and multiply uncontrollably. This uncontrolled unhindered growth results inleads to the formation of tumors. A multitude of elements can induce these mutations, including exposure to harmful agents such as tobacco smoke and air atmospheric pollution. However, it is in NSCLC that where mutations within the p53 gene are most prevalent, affecting up to half of all cases manifest with the greatest most significant frequency, afflicting up to half of all cases [13]. Comprehensive investigation has disclosed that deviations within this particular genetic structure may be correlated with increased tumor progression and resistance to chemotherapy heightened tumor progression and

enhanced resistance to chemotherapy treatments. As a result, Consequently, NSCLC patients suffering from p53 mutations have significantly reduced overall survival exhibit significantly lower prospects for survival as a whole. Moreover, observations have shown unveiled that alterations in this essential gene are predictive of both recurrence rates and metastatic manifestations in individuals who have undergone surgical intervention for their NSCLC condition bear predictive qualities concerning both recurrence rates and metastasis manifestation amongst individuals who have received surgical intervention targeting their NSCLC condition [14]. Overall, the role of the p53 gene in lung cancer as is that it can to guide the expansion of new and effective treatment options for patients' therapy choices for patients. Ongoing research is having been focused focusing on developing therapies that can target mutant mutated p53 protein or reform the role of wild-type p53 in lung cancer cells [15]. In addition, Moreover, screening for p53 mutations and other genetic markers can help identify patients at higher risk for of developing lung cancer or who can aid from personalized treatment strategies [16].

Description of the p53 Gene and Its Functions

The p53 gene is usually located near the short arm of chromosome 17 and is critical crucial for generating a protein called p53 [11]. By binding to DNA and influencing the production of messenger RNA (mRNA), this protein acts as a transcription factor and regulates the expression of other genes [17]. The p53 protein plays has several important essential important roles in normal cells. First, it acts as a checkpoint in the cell cycle, ensuring that cells do not replicate their DNA or divide when there is DNA damage [18]. Under certain circumstances, when If DNA damage is detected, in certain circumstances, p53 has the ability to pause the cell cycle, which provide sing an opportunity for DNA repair. However, if the level of damage is deemed too severe, it can also initiate apoptosis (programmed cell death) [19]. Furthermore, p53 is involved in the activation of various genes related to DNA repair, contributing to this crucial process. Additionally, it regulates the expression of genes associated with angiogenesis, thereby inhibiting the formation of blood vessels necessary for tumor growth and spread [20]. However, when mutations occur in the p53 gene, the resulting protein loses its ability to carry out its usual functions. These mutations are prevalent in cancer and enable damaged cells to persist and proliferate multiply, ultimately leading to tumor formation [21]. The p53 gene and the protein it produces are recognized as significant components of in the body's body's defense against cancer. However, certain specific mutations in this gene are associated with a high risk of developing several types kinds of cancer, containing including lung cancer.

Mutations in the p53 Gene and Their Effects on Lung Cancer

Mutations in the p53 gene are commonly found generally celebrated in different types of cancer, including lung cancer. In the case of NSCLC, it has been found that up to 50% of cases have been found to exhibit p53 mutations. These mutations can occur at various points along the gene and can have varying impacts on the functionality of the resulting p53 protein [22]. Some mutations in the p53 gene can cause the p53 protein to lose its full role, while others may cause a partial loss of function or alter the protein's activity of the protein in a way that promotes cancer development. In some cases, mutations in the p53 gene can lead to result in the production of a truncated or abnormal p53 protein that may have new functions, including the ability to promote cancer growth and metastasis [8]. The effect of p53 mutations on lung cancer is significant, with far-reaching consequences. Mutations in p53 are directly linked to an increased likelihood of aggressive tumor maturation maturing, resistance to chemotherapy treatments, and reduced chances of long-term survival for patients with NSCLC. Additionally, these genetic abnormalities provide useful insight helpful insights into the likelihood of recurrence and metastasis in individuals who have undergone surgical treatment for NSCLC [23]. Emerging evidence suggests that there may be a connection among between p53 mutations and unfavorable results in individuals with NSCLC. However, it has been discovered that mutations may serve as a prognostic indicator for patients who could benefit from immune checkpoint inhibitors. This valuable insight has the potential to inform treatment decisions and ultimately lead to better patients' outcomes for patients [24]. In order to advance

treatments and improve outcomes for lung cancer patients those affected by lung cancer, it is imperative that must gain a comprehensive understanding of the impact influence of p53 mutations on the disease. Ongoing research is exploring innovative ways to target mutant p53 or restore wild-type p53 function in lung cancer cells. This research is critical to the development of effective treatments and progress toward better outcomes for patients Currently, there is ongoing research ongoing research is being conducted to explore innovative methods for targeting mutated p53 or reinstating the function of wild-type p53 in lung cancer cells. This research is vital to the development of effective treatments and progress towards better outcomes for patients. It has been observed that NSCLC often involves genetic alterations in the p53 gene, and various types of mutations have been identified [25], including:

1. Missense mutations: These are the prevalent p53 mutation type that is often observed in lung cancer. The p53 protein's amino acid sequence of the p53 protein is changed by a single nucleotide change in the DNA sequence of the p53 gene, which is the result of missense mutations. The protein may lose function or gain new oncogenic functions depending on the alteration of its structure and function [26].
2. Non-sense mutations: These are mutations that create construct a premature stop codon in the DNA sequence of the p53 gene, resulting in the production of a truncated protein that is usually non-functional [27].
3. Frameshift mutations: Mutations can cause a shift in the reading frame and a truncated or altered protein due to the insertion or deletion of one or more nucleotides in the DNA sequence of the p53 gene [28].
4. Splice site mutations: Abnormal splicing of the mRNA and the production of truncated or altered protein is compelled by mutations in the intron-exon boundaries of the p53 gene [29].
5. Deletions: Loss of one or more exons of the p53 gene can be caused by these large-scale deletions, resulting in the production of a non-functional protein [30].

The type and location of p53 mutations can impact the function of the protein and its role in cancer growth. Some mutations may completely altogether abolish the tumor suppressor function of p53, while others may alter its activity in ways that promote cancer growth and progression. Therefore, predicting disease prognosis and guiding treatment decisions can be achieved disease prognosis can be predicted, and treatment decisions can be made by identifying the kind and place of p53 mutations in lung cancer [31, 32].

p53 Mutations Impact Tumor Development and Advancement

Loss or altered function of the p53 protein due to mutations may cause tumor growth and progression in lung and other cancers [33]. Here are some of the ways in which p53 mutations can affect the maturation and progression of tumors:

1. Increased cell proliferation: The cell cycle is controlled by wild-type p53 by arresting halting cell division in response reaction to DNA damage or other stresses. Alterations in p53 may lead to an unrestricted increase in cell proliferation and the development of tumors. In 2021, Marei HE and colleagues demonstrated promising results for regarding the use of the p53 pathway in the development creation of innovative therapies for lung cancer treatment [34]. Additionally, in 2022, Canale M and colleagues indicated that mutations in p53 can disrupt interfere with cell cycle regulation, resulting in uncontrolled cell proliferation and tumor growth [35].
2. Decreased apoptosis: When there is severe DNA damage or other defects in cells, wild-type p53 has the ability to trigger apoptosis. Mutations in p53 can prevent the induction of apoptosis, allowing damaged cells to survive and potentially become cancerous. Numerous investigations, including studies by Murai et al., (2018) and Wang et al., (2021), have demonstrated that p53 mutations inhibit apoptosis, allowing damaged cells to survive and contribute to cancer development. Murai et al., (2018) found that epidermal tissue adapts to Decreased apoptosis: When there is severe DNA damage or other defects in cells, wild-type p53 can trigger apoptosis. Mutations in p53 can prevent the induction of apoptosis, allowing damaged cells to survive and potentially become cancerous. Numerous investigations, including studies by Murai et al., (2018) and Wang et al., (2021), have demonstrated that p53 mutations inhibit apoptosis, allowing damaged cells to

survive and contribute to cancer development [36, 37]. Murai et al., (2018) found that epidermal tissue adapts to restrain progenitors carrying clonal p53 mutations [36], while Wang et al., (2021) showed that MDM2 inhibition promotes antitumor responses in p53 wild-type cancer cells through their interaction with the immune and stromal microenvironment [37].

3. Carrying clonal p53 mutations [36], while Wang et al., (2021) showed that inhibition of MDM2 promotes antitumor responses in p53 wild-type cancer cells through its their interaction with the immune and stromal microenvironment [37].
4. Genetic instability: The role of p53 in regulating DNA repair mechanisms is crucial for maintaining genetic stability. However, any mutations in p53 can result in genetic instability, which may lead to the accumulation of additional mutations and genomic alterations, ultimately contributing to tumor growth and progression. Several investigations, such as those conducted by Wang and Sun (2017) and Esteban-Burgos et al., (2020), have revealed that mutations in the p53 gene lead to genetic instability and the accumulation of mutations, which promotes tumor progression promoting the advancement of tumors [38, 39]. Wang and Sun (2017) focused on TP53 mutations, expression, and interaction networks in human cancers [38], while Esteban-Burgos et al., (2020) investigated tumor regression and resistance mechanisms upon CDK4 and RAF1 inactivation in KRAS/P53 mutant lung adenocarcinomas [39].
5. Increased angiogenesis: Mutant p53 proteins can promote angiogenesis by stimulating the expression of genes that produce pro-angiogenic factors. Increased angiogenesis can provide a blood supply to the growing tumor and stimulate metastasis increased angiogenesis may furnish the growing tumor with a blood supply and stimulate metastasis. Studies Research by Brown et al., (2019) and Garcia et al., (2020) has shown that mutant p53 proteins can enhance angiogenesis, supporting tumor growth and metastasis [40, 41]. Brown et al., (2019) conducted CRISPR screens in TP53 wild-type cells [40], while Garcia et al., (2020) focused on the regulation of the MDM2-p53 pathway by the ubiquitin ligase HERC2 [41].
6. Resistance to therapy: Mutations in p53 can confer resistance to chemotherapy and radiotherapy, allowing tumor cells to persist and continue to grow and divide. Several studies have indicated that p53 mutations confer resistance to chemotherapy and radiotherapy, thereby compromising impacting the effectiveness of cancer treatment strategies. For example, Aisner DL et al., (2018) found that p53 mutations in lung adenocarcinoma patients with targetable mutations influence treatment outcomes [42]. Additionally, Martinez-Useros J et al., (2021) highlighted the epigenetic mechanisms involved in the development of aggressive solid tumors, shedding light on potential treatment targets [43].

The result of p53 mutations on tumor development and progression advancement are complex and can depend on the specific mutation and the background of the tumor microenvironment. Comprehending the effects of p53 mutations on lung cancer is critical for designing new therapies and improving patients' outcomes for patients [44, 45].

Mechanisms of p53 Inactivation in Lung Cancer

Alterations in the p53 gene could potentially result in a decrease in its effectiveness or altered function of the p53 protein, contributing to the growing growth and progression progress of lung cancer. There are several mechanisms by which p53 can be inactivated in lung cancer, including:

1. Loss of heterozygosity (LOH): It is worth noting that in lung cancer, p53 can become inactive due to the loss or removal of one an allele of the p53 gene. This This It can occur through various mechanisms, including the deletion of the chromosomal region containing that includes the p53 gene, mitotic recombination, or gene conversion [46].
2. Abnormalities in p53 protein expression: Abnormalities in p53 protein expression can also lead to p53 inactivation in lung cancer. Overexpression of MDM2, a negative controller of p53, may lead to increased degradation of the p53 protein, reducing its levels in the cell. Mutations in other genes that control p53 expression or activity, such as p14ARF, can also contribute to p53 inactivation [47].
3. Post-translational modifications: Post-translational modifications of the p53 protein can affect its activity and stability. For example, the process of phosphorylation has been observed to have an

impact on the DNA-binding and gene activation ability of p53. Mutations in genes involved in these modifications can lead to p53 inactivation in lung cancer [48, 49].

4. Interference with p53 signaling pathways: Interference with p53 signaling pathways can also contribute to p53 inactivation in lung cancer. For example, mutations in the ATM and CHK2 genes can affect impair p53 function, by interfering with as they affect DNA damage response pathways that activate p53 [50, 51].

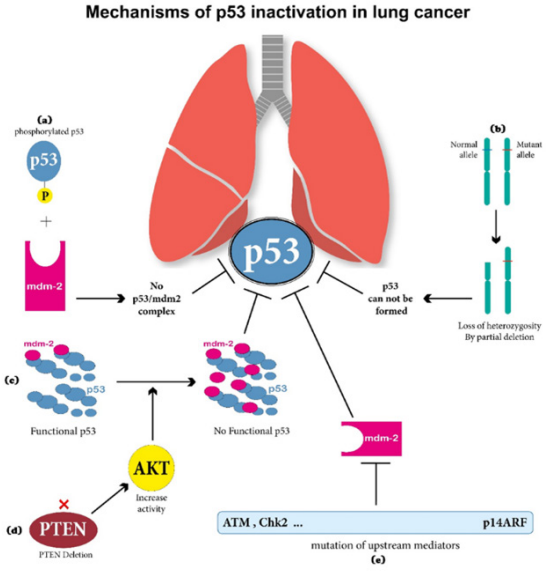

Figure 1: Mechanisms of p53 Inactivation in Lung Cancer
A) Phosphorylation of p53 will disrupt its binding with Mdm2 and p53 is maintained at low level by Mdm2; B) In LOH, one allele of the p53 gene is lost or deleted; C) Abnormal accumulation of the mdm2 protein inhibits p53 function; D) PTEN deletion leads to an increase of AKT activity, and an increase of nuclear mdm2, and impairs p53 response; E) The p53 pathway is inactivated indirectly by mutation of mediators of the p53 pathway and repressing mdm2 protein expression; F) Abbreviations: AKT, The Collective Name of a Set of Three Serine/Threonine-Specific Protein Kinases; ATM, Ataxia Telangiectasia Mutated; MDM2, Mouse Double Minute2; PTEN, Phosphatase, and Tension Homolog

Overall, the inactivation of p53 in lung cancer is a complex process involving various genetic and epigenetic alterations that affect p53 expression, stability, and activity. Understanding Comprehension of these mechanisms is essential for designing new approaches to target p53 and it signaling pathways for the therapy of lung cancer (Figure 1).

Loss of Heterozygosity (LOH)

It is a frequent genetic alteration that occurs in cancer cells, is known as LOH. It refers to the loss or deletion of one copy of a gene in a chromosomal pair of chromosomes that normally generally contains two copies, resulting in a hemizygous state. Deletion of the chromosomal region, including the gene, mitotic recombination, and gene conversion, are among the mechanisms through which LOH can occur [52]. In the context of cancer, LOH typically affects tumor suppressor genes, which typically function to control cancer growth. In the case of p53, LOH is a phenomenon in which where one copy of a gene is lost, leaving only one functional copy in the cell [53]. If the remaining copy of the gene is mutated or deleted, this may affect the failure of the p53 process and contribute donate to the growth and progression advancement of cancer [46]. LOH can be detected by genetic analysis through genetic analyses, such as genotyping or genomic sequencing, and is often used as a feature for the existence of a tumor suppressor gene mutation. LOH analysis is also used to identify sections of the genome that are commonly affected in specific types of cancer, providing insights into the genetic alterations that contribute to cancer expansion and progression advancement [54]. In summary, LOH is a typical mechanism of gene inactivation in cancer, containing in the context of the p53 gene in lung cancer. Understanding the mechanisms and consequences of LOH can inform the expansion of novel cancer diagnosis and therapy approaches.

Abnormalities in p53 Protein Expression

Abnormalities in p53 protein expression can also contribute to the deactivation of p53 inactivation in cancer, including lung cancer. The p53 protein levels are tightly controlled through various mechanisms such as transcriptional regulation, protein stability, and post-translational modifications [47]. Disruptions in any of these mechanisms can lead to altered expression or activity of the p53 protein, contributing to the development and advancement of cancer [55]. One An example of an abnormality in p53 protein expression is the overexpression of MDM2, a negative regulator controller of p53. MDM2 promotes the degradation decay of the p53 protein, leading to decreased levels of p53 in the cell. MDM2 tends to be overexpressed in different kinds of cancer, containing including lung cancer, and this has been connected with an unfavorable prognosis

forecast [56]. In addition to MDM2, mutations in other genes that regulate p53 expression or activity can also contribute to abnormal p53 expression [57]. For example, the p14ARF gene can inhibit MDM2 and stabilize p53 levels. Mutations in p14ARF can lead to reduced levels of p53 in the cell [58]. Post-translational modifications of p53 can also affect its activity and stability. For example, phosphorylation of p53 can affect its capability to bind attach to DNA and trigger target genes. Mutations in genes involved in these modifications can lead to abnormal p53 protein expression and function [59]. Overall, abnormalities in p53 protein expression and stability can contribute to the p53 inactivation of p53 in cancer, including lung cancer. Understanding the mechanisms of p53 regulation and the factors that contribute to abnormal p53 expression can inform the expansion of novel strategies to target for targeting p53 and it signaling pathways for cancer treatment.

Negative Regulators of the p53 Function

There are certain specific proteins or other factors that can hinder the activity of the p53 tumor suppressor protein, which are referred to as negative regulators of p53 function. The p53 protein recreates a highly significant function in preventing the expansion of cancer in normal cells by inducing cell cycle arrest, promoting DNA repair, or triggering programmed cell death (apoptosis) in response answer to cellular stress or damage. The mechanisms used by p53 are essential for maintaining the integrity of healthy cells. The mechanisms that p53 utilizes are essential in maintaining the integrity of healthy cells [51]AºC . In some cases, negative regulators of p53 function in cancer cells can inactivate or suppress affect the inactivation or suppression of p53. This It can ultimately lead to the loss of the tumor- suppressive activities [60]. It is commonly recognized that MDM2 acts serves as a negative regulator of p53. Its interaction with p53 can lead to the promotion of p53's p53's degradation through the ubiquitin-proteasome pathway [61]. MDM2 is frequently found to be overexpressed in different kinds of cancers, including lung cancer. This overexpression can potentially result in decreased levels and activity of p53 [62]. MDMX, also known as MDM4which is also referred to as MDM4, is known to play a role in negatively regulating p53 by inhibiting its transcriptional activity and promoting its degradation, much like the protein MDM2. MDMX is also commonly overexpressed in cancer and may can contribute to p53 inactivation [63]. Other negative regulators of p53 include several protein kinases, such as AKT and cyclin-dependent kinases (CDKs), which can phosphorylate p53 and inhibit its function [64]. The oncogene c-MYC can also repress p53 function by inhibiting its transcriptional activity [65]. In addition to protein factors, epigenetic modifications can also contribute to the inactivation of p53 in cancer. For example, hyper methylation of the p53 gene promoter region may silence p53 expression, while histone deacetylation can inhibit p53 transcriptional activity [66]. Overall, negative regulators of the p53 process can contribute to the inactivation of p53 in lung cancer and other cancers. Understanding the mechanisms and regulation of these negative regulators may provide perspicuity in the expansion of new methods to restore for restoring p53 activity for cancer treatment.

Clinical Significance of p53 Mutations in Lung Cancer

The clinical significance of p53 mutations in lung cancer can be evaluated regarding in terms of their prognostic value and therapeutic implications for treatment [67].

A. Predictive importance of p53 mutations in lung cancer:
   1. Under investigation findings, it has been regarded that the presence of p53 mutations may negatively affect impact the prediction of lung cancer patients with lung cancer in a negative manner negatively, as they are linked with higher rates of tumor recurrence, metastasis, and reduced survival speeds [68].
   2. The presence existence of p53 mutations can also be a useful valuable predictor of reaction to therapy, as patients with p53 mutations may be less likely to respond to certain specific treatments [69].

B. Implications for lung cancer treatment:
   1. The presence existence of p53 mutations may affect the choice of therapy choices for lung cancer patients. For example, chemotherapy and radiation restorative are less effective in patients with p53 mutations, and alternative treatments may need to be considered [70].
   2. Targeted therapies aimed at restoring that aim to

restore or enhancing enhance p53 function may be beneficial for lung cancer patients with p53 mutations [71].

3. The identification of specific p53 mutations in individual patients may also allow for personalized treatment approaches based on the detailed molecular characteristics of their tumors [72, 73].

Overall, the presence existence of p53 mutations in lung cancer has significant clinical substances for both prediction and treatment and highlights the importance of incorporating molecular testing and precision medicine approaches into the guiding implications for both prediction and treatment, and it highlights the importance of incorporating molecular testing and precision medicine approaches into the guidance of lung cancer patients.

Prognostic Value of P53 Mutations in Lung Cancer

Research suggests Investigation results imply that lung cancer patients with p53 modifications may have a less favorable prognosis prediction [74, 75]. These mutations are linked with more elevated speeds of tumor recurrence, metastasis, and decreased survival rates [68]. For example, one study found discovered that patients with NSCLC who have p53 mutations have a worse prognosis than those without. Research has demonstrated that the impact of p53 mutations on survival rates varies between different types of lung cancer. In NSCLC, patients with p53 mutations have been reported to have a median survival rate of 9.9 months, compared to contrasting with a median survival rate of 20.4 months for patients without p53 mutations. On the other hand, it is challenging to compare survival rates between SCLC patients with and without p53 mutations as data regarding SCLC and its correlation with p53 mutations are relatively limited [69, 76]. Another study found that p53 mutations were associated with a higher risk of distant metastasis and decreased overall survival in lung adenocarcinoma patients [77]. However, research into the prognostic implications of p53 mutations in SCLC is ongoing and may provide further insights into their impact on survival outcomes in this specific lung cancer subtype. In addition to overall survival, the presence existence of p53 mutations can also be a useful predictor of response to treatment forecaster of reaction to treatment. For example, research has indicated that individuals with p53 mutations may be less likely to respond to certain chemotherapy regimens specific chemotherapy regimens, such as cisplatin-based regimens therapies [78, 79]. Overall, the predictive importance of p53 mutations in lung cancer highlights the importance significance of molecular testing and precision medicine approaches in guiding treatment decisions and improving patient outcomes.

Implications for Lung Cancer Treatment

The presence existence of p53 mutations in lung cancer can have significant implications for treatment, as these mutations may affect the efficacy of certain treatments and influence treatment decisions [80, 81]. Some of the implications for lung cancer treatment are include:

1. Chemotherapy and radiotherapy radiation therapy: Research has indicated that lung cancer patients' individuals with p53 mutations can have reduced response answer rates to chemotherapy and radiation therapy, compared to patients without these mutations [82]. This It is likely due to the function of p53 in regulating cell cycle arrest and DNA repair in response to DNA damage caused by these treatments [83]. As a result, alternative treatments, such as targeted therapies or immunotherapy, may need to be considered for individuals with p53 mutations.
2. Targeted therapies: New treatments are being developed that to focus on the p53 pathway and may be effective for patients with p53 mutations [84]. For example, PRIMA-1, a small molecule compound, may restore the action of the mutant p53 protein and has shown promising results in preclinical studies investigations [49]. Nutlin-3a is another smallish molecule inhibitor that can activate the p53 pathway path in cells with wild-type p53 and is being investigated in clinical trials preparations for the cure of lung cancer [85].
3. Personalized treatment: The designation of characteristic p53 mutations in individual patients may allow for personalized treatment approaches based on the detailed molecular features of their tumors [86, 87]. For example, as an illustration, individuals with certain p53 mutations can benefit more from targeted therapies than from chemotherapy or radiation cure, and their treatment may be tailored accordingly [88].

In summary, the presence existence of p53 mutations in lung cancer has important implications for treatment, and highlights highlighting the need for personalized and precision medicine approaches that take into account the detailed molecular characteristics features of each patient's tumor.

Novel Therapies Targeting the p53 Pathway

There are currently several novel therapies Several novel therapies targeting the p53 pathway are currently in development for the treatment of cancer, including lung cancer currently, several novel therapies are being developed that target the p53 pathway for the treatment of cancer, including lung cancer. Some of these therapies include:

1. Small molecule inhibitors: Small molecule inhibitors: There are drugs known as small molecule inhibitors that are designed to target specific particular molecules that create a function in the p53 pathway, such as MDM2 and MDM4, which are negative regulators of p53. By inhibiting these molecules, small molecule inhibitors can reform the role of p53 role and cause tumor cell death demise [89]. A number of Numerous promising small molecule inhibitors are presently undergoing clinical trials to investigate their efficacy in treating lung cancer. These include idasanutlin and AMG 232 [90, 91]. Clinical trials studies have investigated the efficacy of small molecule inhibitors targeting MDM2 and MDM4 in restoring p53 function and inducing tumor cell death in lung cancer patients (Liu Y et al., 2019) [92]. Moreover, Cao H et al., (2020) highlighted the role of MDM2-p53 axis dysfunction in hepatocellular carcinoma transformation [93].
2. p53 gene therapy: Gene therapy involves the introduction of introducing a new or modified gene into cells to treat or prevent disease. In the context of lung cancer, p53 gene restoration restorative is a method that involves introducing entails the introduction of a functional copy of the p53 gene into tumor cells. The aim is to correct the role of p53 role and promote cell death demise in a way that is beneficial to the patient [94]. Several types of p53 gene therapy are nowadays being investigated for the treatment cure of lung cancer, including viral vectors and nanoparticle-based delivery systems [95]. Research has explored the use of viral vectors and nanoparticle-based delivery systems for p53 gene therapy in lung cancer, showing promising results in restoring p53 function and promoting cell death (Wang DC et al., 2018) [96]. Chen SY et al., (2021) demonstrated that hyperbaric oxygen therapy suppressed tumor progression by improving tumor hypoxia and inducing tumor apoptosis in lung cancer [97].
3. Nutritional interventions: Nutritional interventions, such as caloric restriction and intermittent fasting, may activate the p53 pathway and potentially induce tumor cell death. [98]. These interventions are thought to work by reducing the availability of nutrients that tumor cells need to grow and survive, which activates the p53 pathway and promotes cell death [99]. Castejón M et al., (2020) have demonstrated the effectiveness of nutritional interventions such as caloric restriction and intermittent fasting in activating the p53 pathway and inducing tumor cell death in preclinical models of lung cancer [100].
4. Combination therapies: Combination Mixture therapies targeting multiple that target numerous pathways involved in cancer growth and survival are also being developed for lung cancer treatment designed for the cure of lung cancer [101]. For example, combining p53-targeted therapies with chemotherapy or radiation therapy may enhance the usefulness of these treatments and decrease the risk of treatment resistance [19, 101]. Clinical trials have evaluated the synergistic effects of combining p53-targeted therapies with chemotherapy or radiotherapy radiation therapy in lung cancer patients, showing improved treatment outcomes and reduced risk of resistance (Patel S et al., 2021) [102]. Moreover, Saleh MN et al., (2021) conducted a phase 1 trial of ALRN-6924, a dual inhibitor of MDMX and MDM2, in patients with solid tumors and lymphomas harboring bearing wild-type TP53, further highlighting the potential of targeted therapies [103].

Overall, targeting the p53 pathway holds promise as an unexplored approach to the therapy of lung cancer and other kinds of cancers. Further research is needed to fully understand the mechanisms of p53 inactivation Further investigation is required to fully comprehend the agents of p53 inactivation comprehend the agents of p53 inactivation fully. Additionally, it is critical paramount to develop safe design secure and practical therapies that target the

p53 pathway.

CONCLUSION

The p53 gene is a crucial tumor suppressor gene that controls cell growth, DNA repair, and apoptosis to prevent cancer development [97]. In lung cancer, the p53 gene is frequently mutated or inactivated, leading to uncontrolled unchecked cell growth and tumor progression advancement [34, 104]. The mechanisms of p53 inactivation in lung cancer include loss of heterozygosity, abnormalities in p53 protein expression, and negative regulators of p53 function [105]. The presence existence of p53 mutations in lung cancer may have predictive importance, and may also affect treatment outcomes. Current Present therapies for lung cancer include contain surgery, radiation therapy, chemotherapy, and immunotherapy, but novel therapies targeting the p53 pathway are also being developed, including small molecule inhibitors, p53 gene therapy, nutritional interventions, and combination therapies [106, 107]. Overall, targeting the p53 pathway holds promise as a novel and innovative method for treating lung cancer and other kinds of cancer, but. However, more studies are needed to design effective and safe treatments that target this pathway.

Future Directions for Research on the p53 Gene in Lung Cancer

Future research on the p53 gene in lung cancer will is likely to focus concentrate on several key areas, including:

Development of new targeted therapies: Current therapies targeting the p53 pathway are still in the early stages of evolution, and more research investigation is needed to identify effective and safe drugs that target this pathway [108].

Understanding comprehending the role of p53 mutations in other types of cancers: while p53 mutations have been well-studied in lung cancer, their function in other kinds of cancers is still being explored. Further investigation is needed to determine the prevalence and impact of p53 mutations in other cancer types [109, 110].

Improving diagnostic tools: Advances in genomic sequencing and other diagnostic tools have improved our ability to detect p53 mutations in lung cancer, but there is still room for improvement. Future research will likely focus on developing more accurate and efficient diagnostic tools for identifying p53 mutations in lung cancer [111].

Overall, continued research on the p53 gene in lung cancer and other types of cancer is essential to improve for improving our understanding of this critical tumor suppressor gene and to develop and developing new and effective treatments for cancer patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

This is a review of the literature and doesn't need an ethical approval number.

REFERENCES

1. Tao M-H. Epidemiology of lung cancer. In: El-Baz A, Suri JS, editors. Lung Cancer and Imaging: Institute of Physics Publishing; 2019. p. 1-15. DOI: 10.1088/978-0-7503-2540-0ch4
2. Barta JA, Powell CA, Wisnivesky JP. Global Epidemiology of Lung Cancer. Ann Glob Health. 2019;85(1). DOI: 10.5334/aogh.2419 PMID: 30741509.
3. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med. 2020;41(1):1-24. DOI: 10.1016/j.ccm.2019.10.001 PMID: 32008623.
4. Schabath MB, Cote ML. Cancer Progress and Priorities: Lung Cancer. Cancer Epidemiol Biomarkers Prev. 2019;28(10):1563-79. DOI: 10.1158/1055-9965.EPI-19-0221 PMID: 31575553.
5. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers. 2021;7(1):3. DOI: 10.1038/s41572-020-00235-0 PMID: 33446664.
6. Corrales L, Rosell R, Cardona AF, Martin C, Zatarain-Barron ZL, Arrieta O. Lung cancer in never smokers: The role of different risk factors other than tobacco smoking. Crit Rev Oncol Hematol. 2020;148:102895. DOI: 10.1016/j.critrevonc.2020.102895 PMID: 32062313.
7. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med. 2020;383(7):640-9. DOI: 10.1056/NEJMoa1916623 PMID: 32786189.
8. Gupta A, Shah K, Oza MJ, Behl T. Reactivation of p53 gene by MDM2 inhibitors: A novel therapy for cancer treatment. Biomed Pharmacother. 2019;109:484-92. DOI: 10.1016/j.biopha.2018.10.155 PMID: 30551517.
9. Duffy MJ, Synnott NC, Crown J. Mutant p53 as a target

for cancer treatment. Eur J Cancer. 2017;83:258-65. DOI: 10.1016/j.ejca.2017.06.023 PMID: 28756138.

10. Zhang C, Liu J, Xu D, Zhang T, Hu W, Feng Z. Gain-of-function mutant p53 in cancer progression and therapy. J Mol Cell Biol. 2020;12(9):674-87. DOI: 10.1093/jmcb/mjaa040 PMID: 32722796.
11. Levine AJ. P53 and The Immune Response: 40 Years of Exploration-A Plan for the Future. Int J Mol Sci. 2020;21(2). DOI: 10.3390/ijms21020541 PMID: 31952115.
12. Xu F, Lin H, He P, He L, Chen J, Lin L, et al. A TP53-associated gene signature for prediction of prognosis and therapeutic responses in lung squamous cell carcinoma. Oncoimmunology. 2020;9(1):1731943. DOI: 10.1080/2162402X.2020.1731943 PMID: 32158625.
13. Tung MC, Lin PL, Wang YC, He TY, Lee MC, Yeh SD, et al. Mutant p53 confers chemoresistance in non-small cell lung cancer by upregulating Nrf2. Oncotarget. 2015;6(39):41692-705. DOI: 10.18632/oncotarget.6150 PMID: 26497680.
14. Zhou Y, Hoti N, Ao M, Zhang Z, Zhu H, Li L, et al. Expression of p16 and p53 in non-small-cell lung cancer: clinicopathological correlation and potential prognostic impact. Biomark Med. 2019;13(9):761-71. DOI: 10.2217/bmm-2018-0441 PMID: 31157548.
15. Hao XL, Han F, Zhang N, Chen HQ, Jiang X, Yin L, et al. TC2N, a novel oncogene, accelerates tumor progression by suppressing p53 signaling pathway in lung cancer. Cell Death Differ. 2019;26(7):1235-50. DOI: 10.1038/s41418-018-0202-8 PMID: 30254375.
16. Zhang T, Li Y, Zhu R, Song P, Wei Y, Liang T, et al. Transcription Factor p53 Suppresses Tumor Growth by Prompting Pyroptosis in Non-Small-Cell Lung Cancer. Oxid Med Cell Longev. 2019;2019:8746895. DOI: 10.1155/2019/8746895 PMID: 31737176.
17. Duffy MJ, Synnott NC, O'Grady S, Crown J. Targeting p53 for the treatment of cancer. Semin Cancer Biol. 2022;79:58-67. DOI: 10.1016/j.semcancer.2020.07.005 PMID: 32741700.
18. Nakamura M, Obata T, Daikoku T, Fujiwara H. The Association and Significance of p53 in Gynecologic Cancers: The Potential of Targeted Therapy. Int J Mol Sci. 2019;20(21). DOI: 10.3390/ijms20215482 PMID: 31689961.
19. Boutelle AM, Attardi LD. p53 and Tumor Suppression: It Takes a Network. Trends Cell Biol. 2021;31(4):298-310. DOI: 10.1016/j.tcb.2020.12.011 PMID: 33518400.
20. Hassin O, Oren M. Drugging p53 in cancer: one protein, many targets. Nat Rev Drug Discov. 2023;22(2):127-44. DOI: 10.1038/s41573-022-00571-8 PMID: 36216888.
21. Bourdon JC. p53 Family isoforms. Curr Pharm Biotechnol. 2007;8(6):332-6. DOI: 10.2174/138920107783018444 PMID: 18289041.
22. Tsao MS, Aviel-Ronen S, Ding K, Lau D, Liu N, Sakurada A, et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. J Clin Oncol. 2007;25(33):5240-7. DOI: 10.1200/JCO.2007.12.6953 PMID: 18024870.
23. Ahrendt SA, Hu Y, Buta M, McDermott MP, Benoit N, Yang SC, et al. p53 mutations and survival in stage I non-small-cell lung cancer: results of a prospective study. J Natl Cancer Inst. 2003;95(13):961-70. DOI: 10.1093/jnci/95.13.961 PMID: 12837832.
24. Wudu M, Ren H, Hui L, Jiang J, Zhang S, Xu Y, et al. DRAM2 acts as an oncogene in non-small cell lung cancer and suppresses the expression of p53. J Exp Clin Cancer Res. 2019;38(1):72. DOI: 10.1186/s13046-019-1068-4 PMID: 30755245.
25. Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. J Biomed Biotechnol. 2011;2011:583929. DOI: 10.1155/2011/583929 PMID: 21331359.
26. Mathe E, Olivier M, Kato S, Ishioka C, Hainaut P, Tavtigian SV. Computational approaches for predicting the biological effect of p53 missense mutations: a comparison of three sequence analysis based methods. Nucleic Acids Res. 2006;34(5):1317-25. DOI: 10.1093/nar/gkj518 PMID: 16522644.
27. Floquet C, Deforges J, Rousset JP, Bidou L. Rescue of non-sense mutated p53 tumor suppressor gene by aminoglycosides. Nucleic Acids Res. 2011;39(8):3350-62. DOI: 10.1093/nar/gkq1277 PMID: 21149266.
28. Tong DR, Zhou W, Katz C, Regunath K, Venkatesh D, Ihuegbu C, et al. p53 Frameshift Mutations Couple Loss-of-Function with Unique Neomorphic Activities. Mol Cancer Res. 2021;19(9):1522-33. DOI: 10.1158/1541-7786.MCR-20-0691 PMID: 34045312.
29. Holmila R, Fouquet C, Cadranel J, Zalcman G, Soussi T. Splice mutations in the p53 gene: case report and review of the literature. Hum Mutat. 2003;21(1):101-2. DOI: 10.1002/humu.9104 PMID: 12497643.
30. Kastenhuber ER, Lowe SW. Putting p53 in Context. Cell. 2017;170(6):1062-78. DOI: 10.1016/j.cell.2017.08.028 PMID: 28886379.
31. Cooper WA, Lam DC, O'Toole SA, Minna JD. Molecular biology of lung cancer. J Thorac Dis. 2013;5 Suppl 5(Suppl 5):S479-90. DOI: 10.3978/j.issn.2072-1439.2013.08.03 PMID: 24163741.
32. Viktorsson K, De Petris L, Lewensohn R. The role of p53 in treatment responses of lung cancer. Biochem Biophys Res Commun. 2005;331(3):868-80. DOI: 10.1016/j.bbrc.2005.03.192 PMID: 15865943.
33. Alvarado-Ortiz E, de la Cruz-Lopez KG, Becerril-Rico J, Sarabia-Sanchez MA, Ortiz-Sanchez E, Garcia-Carranca A. Mutant p53 Gain-of-Function: Role in Cancer Development, Progression, and Therapeutic Approaches. Front Cell Dev Biol. 2020;8:607670. DOI: 10.3389/fcell.2020.607670 PMID: 33644030.
34. Smith AG, Macleod KF. Autophagy, cancer stem cells and drug resistance. J Pathol. 2019;247(5):708-18. DOI: 10.1002/path.5222 PMID: 30570140.
35. Lee SB, Lee S, Park JY, Lee SY, Kim HS. Induction of p53-Dependent Apoptosis by Prostaglandin A(2). Biomolecules. 2020;10(3). DOI: 10.3390/biom10030492 PMID: 32213959.

36. Murai K, Skrupskelyte G, Piedrafita G, Hall M, Kostiou V, Ong SH, et al. Epidermal Tissue Adapts to Restrain Progenitors Carrying Clonal p53 Mutations. Cell Stem Cell. 2018;23(5):687-99 e8. DOI: 10.1016/j.stem.2018.08.017 PMID: 30269904.
37. Wang HQ, Mulford IJ, Sharp F, Liang J, Kurtulus S, Trabucco G, et al. Inhibition of MDM2 Promotes Antitumor Responses in p53 Wild-Type Cancer Cells through Their Interaction with the Immune and Stromal Microenvironment. Cancer Res. 2021;81(11):3079-91. DOI: 10.1158/0008-5472.CAN-20-0189 PMID: 33504557.
38. Wang X, Sun Q. TP53 mutations, expression and interaction networks in human cancers. Oncotarget. 2017;8(1):624-43. DOI: 10.18632/oncotarget.13483 PMID: 27880943.
39. Esteban-Burgos L, Wang H, Nieto P, Zheng J, Blanco-Aparicio C, Varela C, et al. Tumor regression and resistance mechanisms upon CDK4 and RAF1 inactivation in KRAS/P53 mutant lung adenocarcinomas. Proc Natl Acad Sci U S A. 2020;117(39):24415-26. DOI: 10.1073/pnas.2002520117 PMID: 32913049.
40. Brown KR, Mair B, Soste M, Moffat J. CRISPR screens are feasible in TP53 wild-type cells. Mol Syst Biol. 2019;15(8):e8679. DOI: 10.15252/msb.20188679 PMID: 31464370.
41. Garcia-Cano J, Sanchez-Tena S, Sala-Gaston J, Figueras A, Vinals F, Bartrons R, et al. Regulation of the MDM2-p53 pathway by the ubiquitin ligase HERC2. Mol Oncol. 2020;14(1):69-86. DOI: 10.1002/1878-0261.12592 PMID: 31665549.
42. Aisner DL, Sholl LM, Berry LD, Rossi MR, Chen H, Fujimoto J, et al. The Impact of Smoking and TP53 Mutations in Lung Adenocarcinoma Patients with Targetable Mutations-The Lung Cancer Mutation Consortium (LCMC2). Clin Cancer Res. 2018;24(5):1038-47. DOI: 10.1158/1078-0432.CCR-17-2289 PMID: 29217530.
43. Martinez-Useros J, Martin-Galan M, Florez-Cespedes M, Garcia-Foncillas J. Epigenetics of Most Aggressive Solid Tumors: Pathways, Targets and Treatments. Cancers (Basel). 2021;13(13). DOI: 10.3390/cancers13133209 PMID: 34198989.
44. Marei HE, Althani A, Afifi N, Hasan A, Caceci T, Pozzoli G, et al. p53 signaling in cancer progression and therapy. Cancer Cell Int. 2021;21(1):703. DOI: 10.1186/s12935-021-02396-8 PMID: 34952583.
45. Canale M, Andrikou K, Priano I, Cravero P, Pasini L, Urbini M, et al. The Role of TP53 Mutations in EGFR-Mutated Non-Small-Cell Lung Cancer: Clinical Significance and Implications for Therapy. Cancers (Basel). 2022;14(5). DOI: 10.3390/cancers14051143 PMID: 35267450.
46. Zienolddiny S, Ryberg D, Arab MO, Skaug V, Haugen A. Loss of heterozygosity is related to p53 mutations and smoking in lung cancer. Br J Cancer. 2001;84(2):226-31. DOI: 10.1054/bjoc.2000.1528 PMID: 11161381.
47. Takahashi T, Nau MM, Chiba I, Birrer MJ, Rosenberg RK, Vinocour M, et al. p53: a frequent target for genetic abnormalities in lung cancer. Science. 1989;246(4929):491-4. DOI: 10.1126/science.2554494 PMID: 2554494.
48. Chen L, Liu S, Tao Y. Regulating tumor suppressor genes: post-translational modifications. Signal Transduct Target Ther. 2020;5(1):90. DOI: 10.1038/s41392-020-0196-9 PMID: 32532965.
49. Zhu J, Singh M, Selivanova G, Peuget S. Pifithrin-alpha alters p53 post-translational modifications pattern and differentially inhibits p53 target genes. Sci Rep. 2020;10(1):1049. DOI: 10.1038/s41598-020-58051-1 PMID: 31974452.
50. Chen CY, Hsu YL, Tsai YC, Kuo PL. Kotomolide A arrests cell cycle progression and induces apoptosis through the induction of ATM/p53 and the initiation of mitochondrial system in human non-small cell lung cancer A549 cells. Food Chem Toxicol. 2008;46(7):2476-84. DOI: 10.1016/j.fct.2008.04.016 PMID: 18511169.
51. Nuciforo PG, Luise C, Capra M, Pelosi G, d'Adda di Fagagna F. Complex engagement of DNA damage response pathways in human cancer and in lung tumor progression. Carcinogenesis. 2007;28(10):2082-8. DOI: 10.1093/carcin/bgm108 PMID: 17522062.
52. Nichols CA, Gibson WJ, Brown MS, Kosmicki JA, Busanovich JP, Wei H, et al. Loss of heterozygosity of essential genes represents a widespread class of potential cancer vulnerabilities. Nat Commun. 2020;11(1):2517. DOI: 10.1038/s41467-020-16399-y PMID: 32433464.
53. Marsit CJ, Hasegawa M, Hirao T, Kim DH, Aldape K, Hinds PW, et al. Loss of heterozygosity of chromosome 3p21 is associated with mutant TP53 and better patient survival in non-small-cell lung cancer. Cancer Res. 2004;64(23):8702-7. DOI: 10.1158/0008-5472.CAN-04-2558 PMID: 15574780.
54. Nishisaka T, Takeshima Y, Inai K. Evaluation of p53 gene mutation and loss of heterozygosity of 3p, 9p and 17p in precancerous lesions of 29 lung cancer patients. Hiroshima J Med Sci. 2000;49(2):109-16. PMID: 10920577.
55. Steels E, Paesmans M, Berghmans T, Branle F, Lemaitre F, Mascaux C, et al. Role of p53 as a prognostic factor for survival in lung cancer: a systematic review of the literature with a meta-analysis. Eur Respir J. 2001;18(4):705-19. DOI: 10.1183/09031936.01.00062201 PMID: 11716177.
56. Deben C, Deschoolmeester V, Lardon F, Rolfo C, Pauwels P. TP53 and MDM2 genetic alterations in non-small cell lung cancer: Evaluating their prognostic and predictive value. Crit Rev Oncol Hematol. 2016;99:63-73. DOI: 10.1016/j.critrevonc.2015.11.019 PMID: 26689115.
57. Fortunato O, Boeri M, Moro M, Verri C, Mensah M, Conte D, et al. Mir-660 is downregulated in lung cancer patients and its replacement inhibits lung tumorigenesis by targeting MDM2-p53 interaction. Cell Death Dis. 2014;5(12):e1564. DOI: 10.1038/cddis.2014.507 PMID: 25501825.
58. Mounawar M, Mukeria A, Le Calvez F, Hung RJ, Renard H, Cortot A, et al. Patterns of EGFR, HER2, TP53, and KRAS mutations of p14arf expression in non-small cell lung cancers in relation to smoking history. Cancer Res. 2007;67(12):5667-72. DOI: 10.1158/0008-5472.CAN-06-4229 PMID: 17575133.

59. Xing Y, Liu Y, Liu T, Meng Q, Lu H, Liu W, et al. TNFAIP8 promotes the proliferation and cisplatin chemoresistance of non-small cell lung cancer through MDM2/p53 pathway. Cell Commun Signal. 2018;16(1):43. DOI: 10.1186/s12964-018-0254-x PMID: 30064446.
60. Xu Z, Wu W, Yan H, Hu Y, He Q, Luo P. Regulation of p53 stability as a therapeutic strategy for cancer. Biochem Pharmacol. 2021;185:114407. DOI: 10.1016/j.bcp.2021.114407 PMID: 33421376.
61. Ning Y, Hui N, Qing B, Zhuo Y, Sun W, Du Y, et al. ZCCHC10 suppresses lung cancer progression and cisplatin resistance by attenuating MDM2-mediated p53 ubiquitination and degradation. Cell Death Dis. 2019;10(6):414. DOI: 10.1038/s41419-019-1635-9 PMID: 31138778.
62. Putri HE, Nutho B, Rungrotmongkol T, Sritularak B, Vinayanuwattikun C, Chanvorachote P. Bibenzyl analogue DS-1 inhibits MDM2-mediated p53 degradation and sensitizes apoptosis in lung cancer cells. Phytomedicine. 2021;85:153534. DOI: 10.1016/j.phymed.2021.153534 PMID: 33773191.
63. Cheng F, Dou J, Zhang Y, Wang X, Wei H, Zhang Z, et al. Urolithin A Inhibits Epithelial-Mesenchymal Transition in Lung Cancer Cells via P53-Mdm2-Snail Pathway. Onco Targets Ther. 2021;14:3199-208. DOI: 10.2147/OTT.S305595 PMID: 34040386.
64. Jo SK, Hong JY, Park HJ, Lee SK. Anticancer Activity of Novel Daphnane Diterpenoids from Daphne genkwa through Cell-Cycle Arrest and Suppression of Akt/STAT/Src Signalings in Human Lung Cancer Cells. Biomol Ther (Seoul). 2012;20(6):513-9. DOI: 10.4062/biomolther.2012.20.6.513 PMID: 24009843.
65. Nian W, Ao X, Wu Y, Huang Y, Shao J, Wang Y, et al. miR-223 functions as a potent tumor suppressor of the Lewis lung carcinoma cell line by targeting insulin-like growth factor-1 receptor and cyclin-dependent kinase 2. Oncol Lett. 2013;6(2):359-66. DOI: 10.3892/ol.2013.1375 PMID: 24137330.
66. Storozhuk Y, Sanli T, Hopmans SN, Schultz C, Farrell T, Cutz JC, et al. Chronic modulation of AMP-Kinase, Akt and mTOR pathways by ionizing radiation in human lung cancer xenografts. Radiat Oncol. 2012;7:71. DOI: 10.1186/1748-717X-7-71 PMID: 22607554.
67. Campling BG, el-Deiry WS. Clinical implications of p53 mutations in lung cancer. Methods Mol Med. 2003;75:53-77. DOI: 10.1385/1-59259-324-0:53 PMID: 12407735.
68. Scoccianti C, Vesin A, Martel G, Olivier M, Brambilla E, Timsit JF, et al. Prognostic value of TP53, KRAS and EGFR mutations in nonsmall cell lung cancer: the EUELC cohort. Eur Respir J. 2012;40(1):177-84. DOI: 10.1183/09031936.00097311 PMID: 22267755.
69. Jiao XD, Qin BD, You P, Cai J, Zang YS. The prognostic value of TP53 and its correlation with EGFR mutation in advanced non-small cell lung cancer, an analysis based on cBioPortal data base. Lung Cancer. 2018;123:70-5. DOI: 10.1016/j.lungcan.2018.07.003 PMID: 30089598.
70. Dey A, Wong ET, Bist P, Tergaonkar V, Lane DP. Nutlin-3 inhibits the NFkappaB pathway in a p53-dependent manner: implications in lung cancer therapy. Cell Cycle. 2007;6(17):2178-85. DOI: 10.4161/cc.6.17.4643 PMID: 17786042.
71. Kumar S, Mohan A, Guleria R. Prognostic implications of circulating anti-p53 antibodies in lung cancer--a review. Eur J Cancer Care (Engl). 2009;18(3):248-54. DOI: 10.1111/j.1365-2354.2008.01019.x PMID: 19432918.
72. Endoh H, Yatabe Y, Shimizu S, Tajima K, Kuwano H, Takahashi T, et al. RASSF1A gene inactivation in non-small cell lung cancer and its clinical implication. Int J Cancer. 2003;106(1):45-51. DOI: 10.1002/ijc.11184 PMID: 12794755.
73. Yang S, Che SP, Kurywchak P, Tavormina JL, Gansmo LB, Correa de Sampaio P, et al. Detection of mutant KRAS and TP53 DNA in circulating exosomes from healthy individuals and patients with pancreatic cancer. Cancer Biol Ther. 2017;18(3):158-65. DOI: 10.1080/15384047.2017.1281499 PMID: 28121262.
74. Horio Y, Takahashi T, Kuroishi T, Hibi K, Suyama M, Niimi T, et al. Prognostic Significance of p53 Mutations and 3p Deletions in Primary Resected Non-Small Cell Lung Cancer1. Cancer Res. 1993;53(1):1-4. PMID: 8380124.
75. Mitsudomi T, Hamajima N, Ogawa M, Takahashi T. Prognostic Significance of p53 Alterations in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis. Clin Cancer Res. 2000;6(10):4055-63. PMID: 11051256.
76. Schiller JH, Adak S, Feins RH, Keller SM, Fry WA, Livingston RB, et al. Lack of prognostic significance of p53 and K-ras mutations in primary resected non-small-cell lung cancer on E4592: a Laboratory Ancillary Study on an Eastern Cooperative Oncology Group Prospective Randomized Trial of Postoperative Adjuvant Therapy. J Clin Oncol. 2001;19(2):448-57. DOI: 10.1200/JCO.2001.19.2.448 PMID: 11208838.
77. Qin K, Hou H, Liang Y, Zhang X. Prognostic value of TP53 concurrent mutations for EGFR- TKIs and ALK-TKIs based targeted therapy in advanced non-small cell lung cancer: a meta-analysis. BMC Cancer. 2020;20(1):328. DOI: 10.1186/s12885-020-06805-5 PMID: 32299384.
78. Wang F, Zhao N, Gao G, Deng HB, Wang ZH, Deng LL, et al. Prognostic value of TP53 co-mutation status combined with EGFR mutation in patients with lung adenocarcinoma. J Cancer Res Clin Oncol. 2020;146(11):2851-9. DOI: 10.1007/s00432-020-03340-5 PMID: 32743759.
79. Ciancio N, Galasso MG, Campisi R, Bivona L, Migliore M, Di Maria GU. Prognostic value of p53 and Ki67 expression in fiberoptic bronchial biopsies of patients with non small cell lung cancer. Multidiscip Respir Med. 2012;7(1):29. DOI: 10.1186/2049-6958-7-29 PMID: 22978804.
80. Chang YL, Wu CT, Lin SC, Hsiao CF, Jou YS, Lee YC. Clonality and prognostic implications of p53 and epidermal growth factor receptor somatic aberrations in multiple primary lung cancers. Clin Cancer Res. 2007;13(1):52-8. DOI: 10.1158/1078-0432.CCR-06-1743 PMID: 17200338.
81. Ma X, Le Teuff G, Lacas B, Tsao MS, Graziano S, Pi-

gnon JP, et al. Prognostic and Predictive Effect of TP53 Mutations in Patients with Non-Small Cell Lung Cancer from Adjuvant Cisplatin-Based Therapy Randomized Trials: A LACE-Bio Pooled Analysis. J Thorac Oncol. 2016;11(6):850-61. DOI: 10.1016/j.jtho.2016.02.002 PMID: 26899019.

82. Nishizaki M, Meyn RE, Levy LB, Atkinson EN, White RA, Roth JA, et al. Synergistic Inhibition of Human Lung Cancer Cell Growth by Adenovirus-mediated Wild-Type p53 Gene Transfer in Combination with Docetaxel and Radiation Therapeutics in Vitro and in Vivo1. Clin Cancer Res. 2001;7(9):2887-97. PMID: 11555607.
83. Swisher SG, Roth JA, Komaki R, Gu J, Lee JJ, Hicks M, et al. Induction of p53-regulated Genes and Tumor Regression in Lung Cancer Patients after Intratumoral Delivery of Adenoviral p53 (INGN 201) and Radiation Therapy1. Clin Cancer Res. 2003;9(1):93-101. PMID: 12538456.
84. Turrell FK, Kerr EM, Gao M, Thorpe H, Doherty GJ, Cridge J, et al. Lung tumors with distinct p53 mutations respond similarly to p53 targeted therapy but exhibit genotype-specific statin sensitivity. Genes Dev. 2017;31(13):1339-53. DOI: 10.1101/gad.298463.117 PMID: 28790158.
85. Goldstein I, Marcel V, Olivier M, Oren M, Rotter V, Hainaut P. Understanding wild-type and mutant p53 activities in human cancer: new landmarks on the way to targeted therapies. Cancer Gene Ther. 2011;18(1):2-11. DOI: 10.1038/cgt.2010.63 PMID: 20966976.
86. Schneider BJ, Kalemkerian GP. Personalized Therapy of Small Cell Lung Cancer. Adv Exp Med Biol. 2016;890:149-74. DOI: 10.1007/978-3-319-24932-2_9 PMID: 26703804.
87. Salgia R, Hensing T, Campbell N, Salama AK, Maitland M, Hoffman P, et al. Personalized treatment of lung cancer. Semin Oncol. 2011;38(2):274-83. DOI: 10.1053/j.seminoncol.2011.01.012 PMID: 21421117.
88. Yang C, Huang X, Li Y, Chen J, Lv Y, Dai S. Prognosis and personalized treatment prediction in TP53-mutant hepatocellular carcinoma: an in silico strategy towards precision oncology. Brief Bioinform. 2021;22(3). DOI: 10.1093/bib/bbaa164 PMID: 32789496.
89. Chandrasekar D, Tribett E, Ramchandran K. Integrated Palliative Care and Oncologic Care in Non-Small-Cell Lung Cancer. Curr Treat Options Oncol. 2016;17(5):23. DOI: 10.1007/s11864-016-0397-1 PMID: 27032645.
90. Patel S, Player MR. Small-molecule inhibitors of the p53-HDM2 interaction for the treatment of cancer. Expert Opin Investig Drugs. 2008;17(12):1865-82. DOI: 10.1517/13543780802493366 PMID: 19012502.
91. Celegato M, Messa L, Goracci L, Mercorelli B, Bertagnin C, Spyrakis F, et al. A novel small-molecule inhibitor of the human papillomavirus E6-p53 interaction that reactivates p53 function and blocks cancer cells growth. Cancer Lett. 2020;470:115-25. DOI: 10.1016/j.canlet.2019.10.046 PMID: 31693922.
92. Liu Y, Wang X, Wang G, Yang Y, Yuan Y, Ouyang L. The past, present and future of potential small-molecule drugs targeting p53-MDM2/MDMX for cancer therapy. Eur J Med Chem. 2019;176:92-104. DOI: 10.1016/j.ejmech.2019.05.018 PMID: 31100649.
93. Cao H, Chen X, Wang Z, Wang L, Xia Q, Zhang W. The role of MDM2-p53 axis dysfunction in the hepatocellular carcinoma transformation. Cell Death Discov. 2020;6:53. DOI: 10.1038/s41420-020-0287-y PMID: 32595984.
94. Munagala R, Aqil F, Jeyabalan J, Kandimalla R, Wallen M, Tyagi N, et al. Exosome-mediated delivery of RNA and DNA for gene therapy. Cancer Lett. 2021;505:58-72. DOI: 10.1016/j.canlet.2021.02.011 PMID: 33610731.
95. Hasbullah HH, Musa M. Gene Therapy Targeting p53 and KRAS for Colorectal Cancer Treatment: A Myth or the Way Forward? Int J Mol Sci. 2021;22(21). DOI: 10.3390/ijms222111941 PMID: 34769370.
96. Wang DC, Wang W, Zhu B, Wang X. Lung Cancer Heterogeneity and New Strategies for Drug Therapy. Annu Rev Pharmacol Toxicol. 2018;58:531-46. DOI: 10.1146/annurev-pharmtox-010716-104523 PMID: 28977762.
97. Chen SY, Tsuneyama K, Yen MH, Lee JT, Chen JL, Huang SM. Hyperbaric oxygen suppressed tumor progression through the improvement of tumor hypoxia and induction of tumor apoptosis in A549-cell-transferred lung cancer. Sci Rep. 2021;11(1):12033. DOI: 10.1038/s41598-021-91454-2 PMID: 34103583.
98. Kasala ER, Bodduluru LN, Barua CC, Sriram CS, Gogoi R. Benzo(a)pyrene induced lung cancer: Role of dietary phytochemicals in chemoprevention. Pharmacol Rep. 2015;67(5):996-1009. DOI: 10.1016/j.pharep.2015.03.004 PMID: 26398396.
99. Freedman AN, Michalek AM, Marshall JR, Mettlin CJ, Petrelli NJ, Black JD, et al. Familial and nutritional risk factors for p53 overexpression in colorectal cancer. Cancer Epidemiol Biomarkers Prev. 1996;5(4):285-91.
100. Castejon M, Plaza A, Martinez-Romero J, Fernandez-Marcos PJ, Cabo R, Diaz-Ruiz A. Energy Restriction and Colorectal Cancer: A Call for Additional Research. Nutrients. 2020;12(1). DOI: 10.3390/nu12010114 PMID: 31906264.
101. Xue W, Dahlman JE, Tammela T, Khan OF, Sood S, Dave A, et al. Small RNA combination therapy for lung cancer. Proc Natl Acad Sci U S A. 2014;111(34):E3553-61. DOI: 10.1073/pnas.1412686111 PMID: 25114235.
102. Patel S, Petty WJ, Sands JM. An overview of lurbinectedin as a new second-line treatment option for small cell lung cancer. Ther Adv Med Oncol. 2021;13:17588359211020529. DOI: 10.1177/17588359211020529 PMID: 34104228.
103. Saleh MN, Patel MR, Bauer TM, Goel S, Falchook GS, Shapiro GI, et al. Phase 1 Trial of ALRN-6924, a Dual Inhibitor of MDMX and MDM2, in Patients with Solid Tumors and Lymphomas Bearing Wild-type TP53. Clin Cancer Res. 2021;27(19):5236-47. DOI: 10.1158/1078-0432.CCR-21-0715 PMID: 34301750.
104. Sammons MA, Nguyen TT, McDade SS, Fischer M. Tumor suppressor p53: from engaging DNA to target gene regulation. Nucleic Acids Res. 2020;48(16):8848-69. DOI: 10.1093/nar/gkaa666 PMID: 32797160.
105. Açıkalın Çoşkun K, Tutar M, Al M, Gök Yurttaş A, Abay

EC, Yürekli N, et al. Role of p53 in Human Cancers. In: Anwar M, Farooq Z, Tauseef M, Avin Balaji Ragunathrao V, editors. p53 - A Guardian of the Genome and Beyond. London, UK: Books on Demand; 2022. DOI: 10.5772/intechopen.101961

106. Filipczak PT, Leng S, Tellez CS, Do KC, Grimes MJ, Thomas CL, et al. p53-Suppressed Oncogene TET1 Prevents Cellular Aging in Lung Cancer. Cancer Res. 2019;79(8):1758-68. DOI: 10.1158/0008-5472.CAN-18-1234 PMID: 30622117.
107. Chou CW, Lin CH, Hsiao TH, Lo CC, Hsieh CY, Huang CC, et al. Therapeutic effects of statins against lung adenocarcinoma via p53 mutant-mediated apoptosis. Sci Rep. 2019;9(1):20403. DOI: 10.1038/s41598-019-56532-6 PMID: 31892709.
108. Zhu G, Pan C, Bei JX, Li B, Liang C, Xu Y, et al. Mutant p53 in Cancer Progression and Targeted Therapies. Front Oncol. 2020;10:595187. DOI: 10.3389/fonc.2020.595187 PMID: 33240819.
109. Santarpia M, Ciappina G, Spagnolo CC, Squeri A, Passalacqua MI, Aguilar A, et al. Targeted therapies for KRAS-mutant non-small cell lung cancer: from preclinical studies to clinical development-a narrative review. Transl Lung Cancer Res. 2023;12(2):346-68. DOI: 10.21037/tlcr-22-639 PMID: 36895930.
110. Sun H, Liu SY, Zhou JY, Xu JT, Zhang HK, Yan HH, et al. Specific TP53 subtype as biomarker for immune checkpoint inhibitors in lung adenocarcinoma. EBioMedicine. 2020;60:102990. DOI: 10.1016/j.ebiom.2020.102990 PMID: 32927274.
111. Wadowska K, Bil-Lula I, Trembecki L, Sliwinska-Mosson M. Genetic Markers in Lung Cancer Diagnosis: A Review. Int J Mol Sci. 2020;21(13). DOI: 10.3390/ijms21134569 PMID: 32604993.