Chapter

Role of p53 in Human Cancers

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Abstract

TP53 codes tumor protein 53-p53 that controls the cell cycle through binding DNA directly and induces reversible cell-cycle arrest. The protein activates DNA repair genes if mutated DNA will be repaired or activates apoptotosis if the damaged DNA cannot be fixed. Therefore, p53, so-called the "guardian of the genome," promote cell survival by allowing for DNA repair. However, the tumor-suppressor function of p53 is either lost or gained through mutations in half of the human cancers. In this work, functional perturbation of the p53 mechanism is elaborated at the breast, bladder, liver, brain, lung cancers, and osteosarcoma. Mutation of wild-type p53 not only diminishes tumor suppressor activity but transforms it into an oncogenic structure. Further, malfunction of the *TP53* leads accumulation of additional oncogenic mutations in the cell genome. Thus, disruption of *TP53* dependent survival pathways promotes cancer progression. This oncogenic *TP53* promotes cell survival, prevents cell death through apoptosis, and contributes to the proliferation and metastasis of tumor cells. The purpose of this chapter is to discuss the contribution of mutant p53 to distinct cancer types.

Keywords: p53, TP53, mutation, loss-of-function, breast cancer, bladder cancer, liver cancer, brain cancer, osteosarcoma

1. Introduction

Cancer is a disease that occurs as a result of mutations in the genes responsible for the DNA repair, cellular proliferation, and cell cycle checkpoints, resulting from the unbalanced equilibrium of oncogenes and tumor suppressor genes that cause uncontrolled growth and invasive migration of the cells [1]. In healthy cells, DNA damage can be repaired by distinct DNA repair mechanisms and the cell can continue to its normal functions. However, if the repair mechanism is perturbed, cells can not correct the changes caused by mutations. In spite of this, the protein product of this gene can be degraded or during proliferation, checkpoints in the cell cycle detect the mutation and the cell undergoes apoptosis [2]. However, cancer cells are master to inactivate the cell cycle checkpoints by mutations on tumor suppressor genes and to activate tightly regulated proto-oncogenes. Proto-oncogenes are expressed only when required [3]. They are expressed in a controlled manner for cell growth and act as mitogens in healthy cells [4]. Due to their mitogenic roles, most of the mitogenic genes within the genome are upregulated in the case of cancer, and most of these genes are considered as proto-oncogenes. As a result of accumulated mutations on proto-oncogenes, the cell enters an uncontrolled division

pathway [3]. Further at some point, accumulation of mutations in DNA repair mechanisms and tumor suppressor genes suppress cell death mechanisms in tumor cells and oncogenes are upregulated and over-activated in tumor cells. All of these changes cause loss of cell cycle checkpoints to control and DNA repair mechanism's function, and the cell eventually is transformed into a cancer cell [5].

The *TP53*, which is known as the guardian of the genome and is one of the proteins that play the most important role in the cell cycle, was first noticed in animal experiments in 1979 when the tumor tissues were examined [6]. p53, a short-lived protein synthesized by the *TP53* gene in cells, was named "p53," taking its name from its molecular weight of 53 kDa (kilodalton) [7]. p53 is a transcription factor that regulates cell division. Specifically, p53 functions at cell differentiation and initiation of DNA repair mechanism, and is a protein that has a role in suppressing cancer in several organisms [8]. The principal mechanism can be summarized with the understanding that p53 is not always active in typical cells and their activity is minimal in the case of healthy cells. p53 protein is activated only after DNA damage.

There are two important steps in the p53 activation process. In the first step, the half-life of p53 increases dramatically, which means the amount of functional p53 increases and degradation of p53 decreases in the cell, then it is observed that p53 proteins rapidly accumulate within the cell due to the DNA damage as illustrated in **Figure 1**. Thereafter, conformational changes convert the protein into transcriptional regulatory protein form through phosphorylation and enable p53 to be functionally activated. Thus, the increased amount of functional p53 activates DNA repair mechanisms. Normally, when the cells have no DNA damage, the amount of p53 is kept at a low level by protein degradation.

A protein called MDM2 (the murine double minute 2) interferes with p53 and inhibits the function of p53 and sends p53, which function in the nucleus, from the nucleus to cytosol. MDM2 also works as a ubiquitin ligase (**Figure 2**). This function of MDM2 helps the destruction of functional p53 by sending p53 to the ubiquitin proteasomal system (UPS), and the amount of p53 in the cell is reduced [1, 9, 10]. When genomic damage occurs in cells, cell growth halts, p53 stimulates

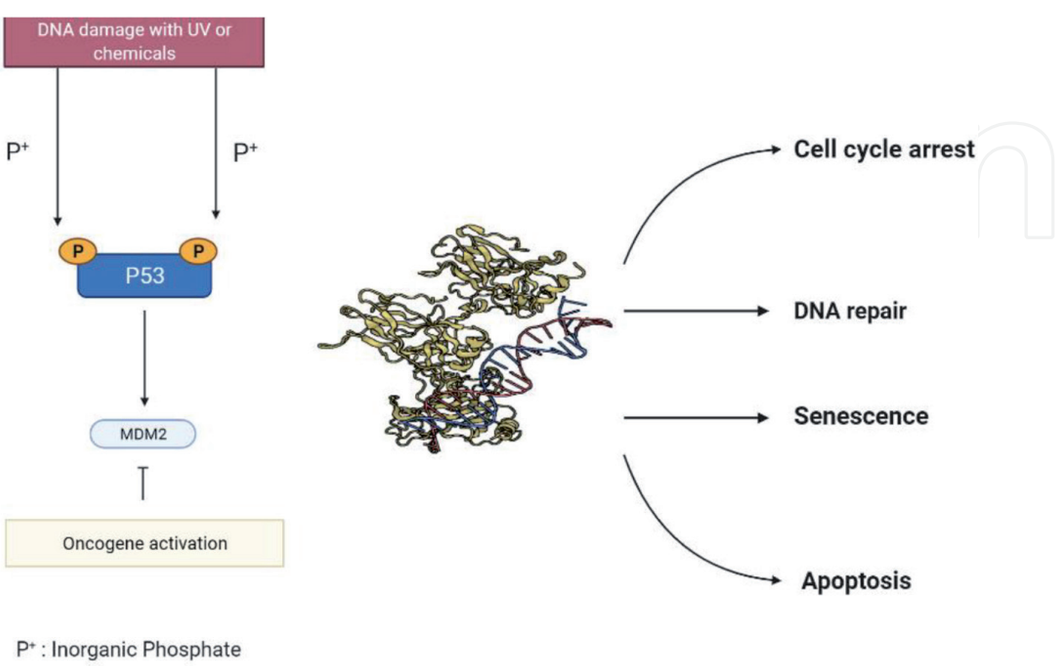

Figure 1.
p53 activation summary; DNA damage enables p53 to become active by inhibition of MDM2 that results in cell cycle arrest, apoptosis, senescence, and DNA repair.

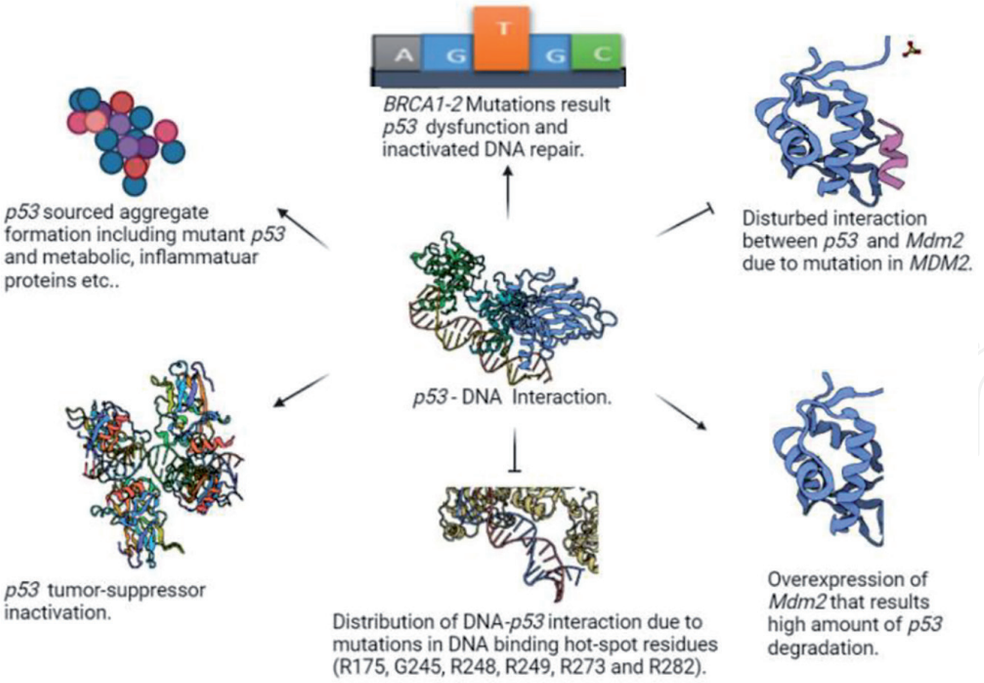

Figure 2.
Overview of inactivation of p53 with distinct mechanisms in breast cancer (MDM2 PDB ID: 1T4F; p53 PDB ID: 1TUP and p63 PDB ID: 3US1).

programmed cell death-apoptosis [11]. Due to its cancer suppression ability, cancer cells adapted to inhibit p53 function in different ways and escape from senescence and apoptosis by distinct mechanisms [10].

These features and changes on the *p53* gene contribute to cancer transformation via escaping from the cell cycle checkpoints and cell death. Therefore, *p53* mutations are crucial for most of the cancer cells to sustain their existence. Observation of high-frequency *p53* mutations in most of the cancerous cell types can be explained in this way [7]. However, it is known that each type of cancer follows different adaptations and genomic rearrangements depending on specific alterations and environmental factors. P53 mutations and functions also change according to the cancer types with distinct mechanisms. This review elaborates on these distinct mechanisms of *p53* mutations in different cancer types.

1.1 Breast cancer

Breast cancer is considered as one of the most frequent types of cancer [12, 13]. Breast cancer morbidity and mortality rates are higher nowadays. There are many different treatment approaches for breast cancer [14]. However, breast cancer in different patients has a variety of symptoms, disease progression, and drug response which proved that breast cancer subtypes are distinct and need different treatment regimens. Breast cancer has a heterogenic nature. Thus, heterogeneity creates different clinical features in the cancer cells [15]. Breast cancer can show differences in the expression of the hormonal receptor as the result of different genetic alterations and rearrangements within the cell [16]. These differences cause different subtypes of breast cancer that show different strategies to survive. With the help of gene expression analysis (genome sequencing, transcriptional and translational analysis, etc.), luminal ER-positive (luminal A and luminal B), HER2 enriched, and triple-negative (basal-like) types are identified as three major types of breast cancer [17].

Mutant *p53* plays a pivotal role in the prognosis of approximately 23% of breast cancer [18]. TP53 mutations are the most common genetic modifications in breast carcinomas, according to recent next-generation sequencing-based research, accounting for 30% of them. On the other hand, the distribution of these mutations is strongly associated with tumor subtypes. In 26% of luminal tumors (17% of luminal A, 41% of luminal B), 69% of molecular apocrine tumors, and 88% of basal-like carcinomas, mutations have been elucidated [19]. Further, protein kinases such as CHK1, CHK2 (Rad53), ATM (ataxia-telangiectasia mutated), and ATR (Rad53-related protein), which respond to DNA damage sentinels, such as BRCA1, also control p53 activity and stability. The kinases directly phosphorylate p53, affecting its instability and function [20].

Although the general prevalence of p53 mutation in breast cancer is around 20%, specific forms of the cancer are associated with greater rates (**Figure 2**). A number of studies, for example, have found an elevated rate of p53 alterations in malignancies caused by carriers of germline BRCA1 and BRCA2 mutations. Surprisingly, p53 mutation occurs in 100% of instances of typical medullary breast carcinomas. This is particularly interesting because it is now well accepted that medullary breast tumors exhibit clinicopathological characteristics with BRCA1-associated instances. Furthermore, methylation-dependent BRCA1 silencing is frequent in medullary breast tumors [21].

TP53 mutation is found in nearly half of HER2 amplified malignancies [13]. The type of change is clearly linked to the breast cancer subtype, with a higher frequency of substitutions in luminal tumors, resulting in a p53 protein with possible novel functionalities such as p63 inactivation. p63 is a member of the p53 family that also has a tumor suppressor activity [22]. The majority of mutations focused on missense mutations. The most frequent missense mutations in p53 are located within the DNA binding domain. Especially in six frequent "hotspot" amino acid codons (R175, G245, R248, R249, R273, and R282) (**Figure 2**) [23].

Some mutant *p53* in the cancer cells lose its tumor-suppressive activity of the wild-type *p53* and shows strong oncogenic functions, defined as a gain of function that provides a selective advantage during tumorigenesis progression [24]. Most of the p53 mutations are seen in the DNA binding domain that allows the expression of DNA repair system proteins [25].

Also, due to mutations, p53 can act like prions and cause accumulation within the cancer cells by binding other proteins, such as metabolism, RNA processing, and inflammatory response [18]. On the other hand, deregulation of MDM2-p53 pathway due to amplification and overexpression of *MDM2* oncogene which is a master regulator of the *p53* tumor suppressor activity, and mutations or deletions of *p53* has been correlated to the initiation, progression, and metastasis of breast cancer [10].

Mutations in TP53, as well as the deletion of RB1 and CDKN2A, are among the most well-known genetic changes in tumor suppressor genes in basal-like breast cancer and triple-negative breast cancer [20]. Indeed, up to 80% of basal-like breast cancer have TP53 alterations, which include nonsense and frameshift mutations. The RNA of 99.4% of basal-like breast cancer patients had TP53 mutant-like status. TP53 mutations may have varied effects depending on the breast tumor subtypes. There is now evidence that inactivation of *p53* by mutation, amplification of MDM2 or MDM4, or infrequent alterations in other p53 pathway components causes luminal cancers [26].

In conclusion, the activity of p53 can be inhibited by either mutation in *p53* or mutations in *p53*-interacted proteins that regulate its function.

1.2 Bladder cancer

Up to 50% of cancer cases have acquired a mechanism that inactivates p53 function to bypass apoptosis. The most indisputable fact about p53 is its high frequency of modifications in human cancer. Mutant p53 proteins form a complex family of several 100 proteins with heterogeneous properties. The *p53* tumor suppressor gene located on chromosome. 17p13 is one of the most frequently mutated genes in all human malignant diseases, including bladder cancer [27].

It is known that p53 gene mutations occur early in the pathogenesis of bladder cancer and late in other cancer types [28, 29]. Tumor protein *p53* gene mutation is an important marker for bladder cancer progression and is associated with poor prognosis and recurrence [30]. The *TP53* gene is responsible for maintaining genome integrity as it encodes a protein that is activated in response to cellular stress to repair possible DNA damage [31].

About 60% of bladder cancer cases result in *mutp53* (mutant-p53) in exon 5–11. *mutp53* is commonly associated with the *mutRb* gene in high-grade, invasive, and poorly prognostic bladder cancer [32]. Up to 20% of all BC cases were caused by the p53 gene mutation in exons 1–4, accompanied by *mutCDKN2a* and loss of ARF function. Therefore, it has been suggested that mutations in the *RB*, *CDKN2a,* and *ARF* genes may follow the *p53* mutation [33].

1.2.1 p53 mutations in bladder cancer

The *p53* gene is mutated in 20–60% of bladder tumors. Especially codon 80 and codon 285 are the regions where mutations are the most common. The gene encodes *p53* has a conserved sequence and has 5 polymorphisms that are located in coding part of the gene. While four of them are codon 34, 36, 47, 72 in exon 4; one was found in exon 6 codon 213. Most of the polymorphisms in *p53* were found in the intronic region. There are two in intron 1, one in intron 2, one in intron 3, two in intron 6, five in intron 7, and one in intron 9. Of these, polymorphisms at codon 72 and codon 47 are well characterized [34].

Codon 280 and 285 in exon 82 are hot regions for mutation formation. Codon 280 is common in 1.2% of all cancer types and mutant in 5.1% of urinary bladder cancers. These values are 0.82% of all cancer types for codon 285, compared to 4.3% of urinary bladder cancers [35].

1.2.2 p53 polymorphisms in bladder cancer

The incidence of the codon 72 arginine/proline (Arg-CGC/Pro-CCC) polymorphism varies by ethnic group and geography [36]. The region containing the five repeat pxxp sequence (proline) located between amino acids 61 and 94 in *p53* is thought to be involved in the signal transduction of this motif through its binding activity to the SH3 region. In cell culture studies, defects in the suppression of tumor cell growth by *p53* have been associated with the deletion of the proline-rich region. Conversion of the G base to the C base causes the conversion of arginine AA at codon 72 to proline AA. The Arg carrying a form of *p53* was found to be significantly more associated with tumor growth than the proline carrying form [37]. In a study, it was shown that the Arg/Arg genotype increases the risk of developing bladder cancer [38]. In addition, Kuroda et al. found an increased risk of urethral cancer in smokers with the Pro/Pro genotype [39].

Silent mutations at codon 36 (CCG → CCT); It was observed that *MDM2* decreased the affinity of TP53 mRNA and decreased the activity of *P53* in apoptosis.

Three similar polymorphisms, D21D (GAC → GAT), P34P (CCC → CCA), and P36P (CCG → CCA), are found in key regions in MDM2-binding TP53 mRNA. According to the latest findings, translation inhibition is inhibited by microRNA (miRNA) targeting gene coding sequences [40, 41].

1.3 Brain cancer

There are more than a 100 different types of brain tumors which are either primary brain tumors that arise from the central nervous system (CNS) cells or secondary brain tumors that have metastasized from other tissues in the body. While primary brain tumors make up about 2% of all cancers, secondary brain tumors are seen 10 times more often.

Brain tumors can be considered as a heterogeneous group of benign and malignant tumors. Even though most types are cancerous, benign tumors can also become damaging for the brain tissue. Their classification using various parameters and a grading system (I–IV) by the World Health Organization (WHO) is a helpful criterion when choosing the best approach in diagnosis and treatment. When classifying brain tumors, in addition to histological criteria, molecular genetic alterations are also taken into consideration and nomenclatured accordingly [42, 43].

Meningiomas, originating in the dura, are usually benign and can be removed by surgery; they represent around 36% of all primary brain tumors [43]. Almost 75% of malignant primary tumors and 29% of all brain tumors are gliomas. They originate from glial cells and are grouped as circumscribed (grade I) and diffusely infiltrating (grades II, III, and IV) gliomas. Circumscribed gliomas, called ependymomas, are usually benign and can be cured with complete resection. They make up about 7% of gliomas and mostly affect children. The latter group, including astrocytomas (about 75% of gliomas) and oligodendrogliomas (about 6% of gliomas), are usually malignant and difficult to cure. This group also includes mixed gliomas which are not easy to diagnose as the composition of cell type, whether astrocytes or oligodendrocytes, may not be accurately determined [42–44]. As the most common and deadly primary tumor, glioblastoma makes up almost half of all gliomas and about 80% of malignant gliomas. About 30% of glioblastomas have *p53* mutations related to loss or gain-of-function, and also dominant-negative effects [45].

One of the most studied proteins, *p53* is best known for its tumor suppressor role. In cases of tumor stress, it stops the cell cycle to either let DNA repair itself or cause cell death with interferes with tumorigenesis. Its involvement plays a major role in the regulation of apoptosis and therefore cases of *p53* mutations lead to deregulation and dysfunction of apoptotic responses through *p53*-dependent mechanisms. It is already one of the most common mutant genes in human cancers, but it is also known to be closely involved with cancers related to CNS, and also other neurological diseases including Alzheimer's disease, Parkinson's disease, and Huntington's disease [46, 47]. Studies done with transgenic mice overexpressing amyloid-β have demonstrated increased expression and accumulation of *p53* in the brain, which was also seen in the brains of Alzheimer's patients [48, 49].

p53 has also been of great importance during the development of the brain and regulation of neuroinflammation [47, 50]. One of the earliest studies performed on *p53*-deficient mice has demonstrated abnormal brain development. As a result of decreased apoptosis, defects in the closing of the neural tube have occurred. This disruption has eventually led to exencephaly followed by anencephaly [51].

Inactivation of *p53* happens through several mechanisms including the disruption of its gene expression or protein stability and also loss or mutation of the gene itself. These mechanisms result in malignant properties such as invasiveness, undifferentiated status, and genetic stability. The frequency of *p53* mutations depends on

the type of tumor. Glioblastoma, the most lethal one, has the highest incidence of 70%. Mixed gliomas and astrocytomas are moderate, 40%, and 50%, respectively. Oligodendrogliomas have the lowest incidence among all gliomas. In general, tumor grades are determinant in the occurrence rate of *p53* mutations, of which missense mutation is the main one. C:G → A:T mutation is the most common mutation of *p53* seen at CpG sites, affecting the DNA binding properties through three codons, R248, R273, and R175, in the DNA binding domain according to The Cancer Genome Atlas (TCGA). Mutations of this domain have led to gain-of-function to induce tumorigenesis. Additionally, splice site mutations, promoter methylations have also been identified [44, 47, 50].

An example of gain-of-function mutation is given in a recent study done on an invasive brain tumor, glioblastoma. Mutation in *TP53* increases the tendency of aggregate formation via mutant *P53* oligomerization due to exposed hydrophobic parts. Once aggregation of this protein takes place in the cell, conditions for cancer initiation and oncogenic activities are likely to be established [52].

Another group analyzed the key genes and pathways of *p53* mutations in low-grade glioma patients. RNA-seq data from the TCGA database were analyzed by various bioinformatics tools to have a deeper understanding of the role of this protein in disease progression. Out of 508 patients, 49% had mutations such as amplification, deletion, truncation, in-frame mutations, and missense mutations throughout the whole gene. Cancer cells with these mutations were then found to be resistant to some chemotherapeutic drugs that are normally used to treat glioma. This is an indication that it is especially important to distinguish whether the patient has *p53* mutation or not to avoid failure of the therapy. In addition, 1100 differentially expressed genes were identified, of which most were associated with pathways related to cancer development and progress [53].

In conclusion, primary brain tumors are difficult to deal with, in terms of understanding their basis and managing the progress. In cases of relevant *p53* mutations, attention can be focused on avoiding the degradation of this protein or using chaperones to reestablish its structural integrity and biological activity. Upstream and downstream molecules can be alternatively targeted to develop other novel therapeutic strategies. Last but not the least, determination of *p53* mutations is a significant step that helps to choose the best individualized therapy for cancer patients.

1.4 Liver cancer (hepatocellular carcinoma)

Liver cancer is the second most common cause of cancer-based mortality worldwide, accounting for 7% of all cancers with 854,000 new diagnoses each year. The main histological subtype of liver cancer is hepatocellular carcinoma (HCC) which originates from hepatocytes. Considering the population, the incidence of hepatocellular carcinoma increases with age, and male individuals are at greater risk. Based on etiological data in HCC; hepatitis virus and HIV infections, smoking and alcohol use, aflatoxin B1 exposure, and metabolic diseases are the factors associated with carcinogenesis. More effective therapies are still being investigated for HCC due to the fact that the methods used in the treatment are less effective, the treatment is accompanied by cirrhosis, liver failure, and the difficulty of grading-staging of the tumor [54, 55].

The functioning of hepatocellular carcinoma induced by carcinogens is caused by multiple dysfunctions on the MDM2-p53 axis. Oncogene activation, genotoxic and ribosomal stress, and hypoxia signals activate the *p53* mechanism. *p53*, the most important tumor suppressor, is also associated with hepatocyte proliferation and metabolism. Hepatitis B virus-X protein (HBx), which binds *p53* and sends

it from the nucleus to the cytoplasm, has been shown to play an important role in the development of HCC. Special regions in MDM2 and *p53* are linked to exposure to environmental carcinogens and the development of HCC. Mutations in the MDM2-p53 axis and chronic HCV infection have been shown to trigger the development of HCC [56]. Normally, if MDM2-p53 key regions are not phosphorylated, the increase in MDM2 levels leads to inhibition of *p53* expression activity, which disrupts cell cycle control and stimulates tumor formation. The scientific findings accumulated due to these mechanisms indicate that *p53* is critical for stopping the development of HCC [8, 57].

Clinical case studies suggest that control of *p53* expression for regeneration of liver tissue after partial hepatectomy may regulate CDK2-CDK4 activity, which promotes DNA synthesis in hepatocytes. In addition, in mice with *p53* defects, repair of liver failure and hepatocyte damage is delayed. According to these results; homeostasis of wild-type *p53* expression controls the proliferation and apoptosis of normal hepatocytes. However, mutant *p53* is predominantly a negative inhibitor compared to wild-type *p53*. The fact that mutant *p53* oncogenic potential is a major factor in liver cancer, as with many malignant cancers [8, 54].

The basic mechanism of apoptosis formed by *p53* depends on death signals that directly or indirectly target mitochondria through pro-apoptotic members of the TP53 and Bcl-2 family, both of which have mutations. Healthy liver cells are resistant to *p53*-mediated cell death, and the relationship between mitochondrial translocation of *p53* and apoptosis after DNA damage is rare. In HCC cells, the activation of *p53* encourages stopping the cell cycle instead of apoptosis, and mostly in hepatocytes, the mitochondrial-dependent *p53* apoptosis pathway is blocked. The likely cause of this critical change is the increased expression of hepatic insulin-like growth factor binding protein-1 (IGFBP1), which antagonizes the mitochondrial *p53* pathway and prevents apoptosis as a result of *p53* activation [58, 59].

The main mutation of TP53 in hepatocellular carcinoma occurs in the DNA binding region of *p53*, which causes a lower affinity to bind specific response units of their targeted genes to the array, and *p53*-mediated MDM2 induction decreases. As a result, misregulation of MDM2 results in high levels of mutant *p53* expression in many cancerous cells [58, 60].

The key role of *P53* in tumor development has made *p53* an inspiring target for drug studies that inhibit HCC development. Treatments to restore *p53* function in HCC have been shown to damage cancer cells that express both mutant *p53* and wild-type *p53*. Current treatment approaches for HCC; chemotherapy, radiotherapy, degradation pathways of ADP-ribosylation factor proteins inhibiting *p53*, inhibition of MDM2-p53 connectivity, and the addition of molecules regulating the active region of the *p53* protein [61].

1.5 Osteosarcoma

Osteosarcoma, which can also be called osteogenic sarcoma, is a cancer type that is related to bones. It is a common pediatric bone tumor as it has an annual diagnose rate of 400 children [62]. This type of cancer starts to form when there is a problem with the cells that are responsible to make new bones [62]. Healthy bone cells may have alterations in their DNA, which can result to make new bones when there is no need for them. As a result of making new bones without a need, there will be a cell mass formed with poorly formed bone cells. Then, this cell mass will destroy the body tissue that was healthy in the first place by invading it. Also, as the cancer progress, some cells can spread through the body and metastasize.

There are two kinds of *p53* with different effects on osteosarcoma. Wild-type *p53* functions as a tumor suppressor and the mutant *p53* have a carcinogenic effect and are found to be overexpressed in malignant osteosarcoma [63]. A study proves this overexpression point by using immunochemistry and concluding that mutant *p53* had a 47.7% positive expression rate [63]. On the other hand, since wild-type *p53* is a protein known to be a tumor suppressor, it is expected to have changes due to mutations, etc. in most cancers. With this change process, a response to DNA damage cannot be made and the genome destabilizes. Like other types of cancer, osteosarcoma is also known to have this type of relationship with the *p53* protein. Changes in *p53* are shown to have a correlation with the instability of the genome with osteosarcoma patients [64]. HDM2 is a protein that functions as a negative regulator of *p53* [64]. It is found that if there is an amplification of the HDM2 protein, the expected instability of the genome does not happen. When HDM2 protein amplification happens without mutations happening in *p53* protein, there is not a high level of instability in the genome. When these direct and indirect ways to change *p53* are compared, the alterations that happen with HDM2 amplification do not even correspond to half of the alterations that destabilize the genome caused by a direct mutation in *p53* [64]. So, this implies different ways that cause a change in the *p53* protein happens to create different results. Since this is not a fully established subject, future studies on the different kinds of changes can be found helpful in the research of this disease and its treatments.

TP53 is a gene that works to help assemble the *p53* (or TP53) protein. The prognostic values of osteosarcoma patients with TP53 mutations are also studied. An analysis was made using eight eligible studies which in total had 210 osteosarcoma patients [4]. Final data from this analysis concluded that in two-year survival of osteosarcoma patients, the mutations of TP53 had a negative impact when compared to wild-type ones. So, it is concluded that TP53 mutations are important for the patients' survival rates and are prognostic markers [65]. Although the results from this study conclude that the mutations have an unfavorable impact on survival, there is still a need for larger-scale studies showing three-to-five-year survival of osteosarcoma patients.

The influence of *TP53* mutations is also shown in another study, St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project (PCGP), which concludes that 90% of the patients with osteosarcoma showed a mutation in the *TP53* gene [66]. This study also revealed the type of mutations upon whole-genome sequencing 34 osteosarcoma tumors [66]. They concluded that 55% of the *TP53* mutations are caused by structural variants, and it is found to be second cancer with these types of mutations that is related to the rearrangement of chromosomes instead of point mutations [66]. This effect of TP53 mutations is believed to be the reason for the ineffectiveness of standard doses in radiation therapy.

1.6 Lung cancer

The TP53 gene mutation is one of the most common causes of lung cancer and has a key role in the carcinogenesis of lung epithelial cells. Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are two main types of lung cancer in humans. Approximately 80% of all lung cancers are NSCLC that creates most of the *TP53* mutations [67].

The TP53 gene has been found in lung cancer pathogenesis with the frequent detection of loss of heterozygosity (LOH) at the location of the *TP53* gene on chromosome 17p13 in lung cancer cell lines and tumor samples. Additionally, it has been shown that the mutations in the TP53 in lung cancers have been linked to a

poorer prognosis and increased cellular resistance to therapy [68]. SCLC specimens have the highest prevalence of *TP53* mutations [69]. However, in NSCLC tumor samples, squamous cell carcinomas have the highest frequency of *TP53* mutations and adenocarcinomas have the lowest frequency. The location of *TP53* mutations is mostly in the DNA-binding domain of TP53 and is detected in cancers with and without allele loss at 17p13 [70]. Acquired *TP53* mutations are kept during tumor progression and metastatic spread since *TP53* coding mutations appear early in the evolution of lung cancer and are possibly essential for maintaining the malignant phenotype. Chang and his colleagues clarified that *TP53* mutations were found in 23.2% of primary tumors and 21.4% of metastatic lymph nodes. Moreover, there was 92.9% concordance between 56 patients with NSCLC who had surgical resection in primary tumors and metastatic lymph nodes [71]. This explains that the majority of *TP53* mutations arise before the tumor spreads. They are subsequently preserved throughout the rest of the tumor's development, therefore there is no selection for *TP53* mutations during metastasis [67].

1.6.1 Tobacco-associated lung cancer and TP53 mutations

Tobacco smoking is the major cause of lung cancer, and the risk of lung cancer rises with the number of cigarettes smoked and the length of time spent smoking although 15% of men and 53% of women with lung cancer in the world are never smokers. Furthermore, in the United States and the European Union, tobacco smoking is responsible for more than 90% of lung cancer in males and 74–80% of lung cancer in women [72]. *TP53* mutations are detected in more than half of lung cancers. Therefore, this makes the *TP53* gene one of the most common targets of tobacco smoking-related DNA alterations.

Several studies have previously discovered hotspots on the *TP53* gene, with G:C to T:A (G to T) transversions being a common finding in tobacco-related lung cancer [73]. In addition, 90% of the guanines that undergo these transversion events are found on the non-transcribed DNA strand. There was a lower incidence of G to T transversions in lung cancer tissues from never-smokers than from smokers [74]. Polycyclic aromatic hydrocarbons (PAH) that are found in tobacco smoke are thought to cause the spectrum of G to T transversions. The major metabolite of benzo[α]pyrene which is the most studied member of the PAH class is benzo[α] pyrene diol epoxide (BPDE). Moreover, it is one of the most dangerous carcinogens found in high concentrations of tobacco smoke [75]. A number of studies have demonstrated that BPDE-DNA adduct patterns in the *TP53* gene in bronchial epithelial cells correspond to G to T mutational hotspots at codons 157, 248, and 273. At these codons, G to T transversions are common for bulky adduct-producing mutagens, such as PAHs and BPDE adducts [76].

1.6.2 TP53 mutations in never-smokers and smokers

Several studies have clarified that lung cancer from smokers shows a different and unique mutation spectrum in the *TP53 gene* than lung cancer from never-smokers. Up to 83% of *TP53* mutations were transitioned in female never-smokers with adenocarcinoma patients. On the other hand, *TP53* mutations in smokers were mostly transversions (60%) and deletions (20%). The incidence of TP53 mutations was shown to be proportional to the amount of tobacco smoking in patients with adenocarcinoma [77]. However, never-smokers with adenocarcinoma patients have more mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase than tobacco-associated lung cancer patients and have a higher response to its inhibitors. Additionally, in adenocarcinoma, *TP53* mutations have been found to

be closely linked to smokers, while EGFR mutations are statistically substantially more common in females and never-smokers. Moreover, the incidence of K-ras and *TP53* mutations varies between never-smoker lung cancer patients and smoker lung cancer patients [78].

1.6.3 Therapeutic strategies for NSCLC patients with TP53 mutation

TP53 mutations show chemoresistance to lung cancer cells *in vivo* and *in vitro*, according to several studies. If TP53 status is determined, chemo or radiation therapy can be decided. For example, cancers carrying the mutant *TP53* are known to be more resistant to ionizing radiation than tumors containing the wild-type *TP53* [79]. To target the TP53 pathway in cancer, virus-based therapeutic strategies are one of the most advanced strategies. Because *TP53* mutations are common in lung cancer, the treatment with various chemotherapy classes and *TP53* gene replacement techniques has been investigated in both preclinical and clinical settings. When *TP53* gene therapy was studied in lung cancer patients in clinical trials, some researchers have suggested that combining adenovirus (Adp53) gene therapy with chemotherapy medicines and radiotherapy can be effective [80]. For instance, 28 patients with NSCLC were given the *Adp53* gene into their tumors without any other therapy in the phase I clinical trial. Two patients (8%) had a significant reduction in tumor size, and 16 patients (64%) had disease stabilization; the remaining seven patients (28%) had disease progression [81].

There are also several approaches such as rational design and screening of chemical libraries to identify small compounds that target mutant *TP53*. RITA was discovered in the National Cancer Institute's (NCI) drugs that could reduce cell proliferation in a wild-type TP53-dependent way. It reactivates TP53 and promotes apoptosis by breaking the interaction with HDM-2 after attaching to it [82]. As a result, it has been proposed as a crucial drug to target tumors with wild-type TP53 that may be resistant to drugs that restore mutant TP53 activity, such as PRIMA-1 (p53 reactivation and production of large apoptosis). PRIMA-1 that is a low-molecular-weight drug has been discovered to suppress the growth of tumor cells expressing mutant *TP53*. It binds to the core of mutant *TP53*, restoring its wild-type conformation and inducing apoptosis in human tumor cells [83]. A study revealed that although PRIMA-1 did not cause apoptosis in human NSCLC cell lines encoding distinct TP53 proteins, such as A549 (p53wt), LX1 (p53R273H), and SKMes1, it did dramatically impair cell viability (p53R280K). In addition, PRIMA-1 enhances adriamycin-induced apoptosis in A549 and LX1 cells when used in combination with the drug. In a preclinical setting, *Adp53* gene therapy and PRIMA-1 which can restore the transcriptional function of mutant TP53, or RITA, which inhibits MDM2-directed TP53 degradation, have been performed, and some of these techniques are now in clinical development [84]. Last but not least, the combination of the traditional and molecular-targeting cancer treatments with new TP53-based therapeutic methods for NSCLC can offer great potential for targeting only cancer cells.

2. Conclusions

P53 stands at the heart of the cancer mechanism due to its role in cell survival and death. *TP53* essential role in cell fate decision attracts the interest of cancer researchers and makes the protein a superior target for anti-cancer drugs. Therefore, the focus on TP53 research at distinct cancer types increases dramatically and TP53 is targeted by drug designers to inhibit its mutant protein function. *P53*

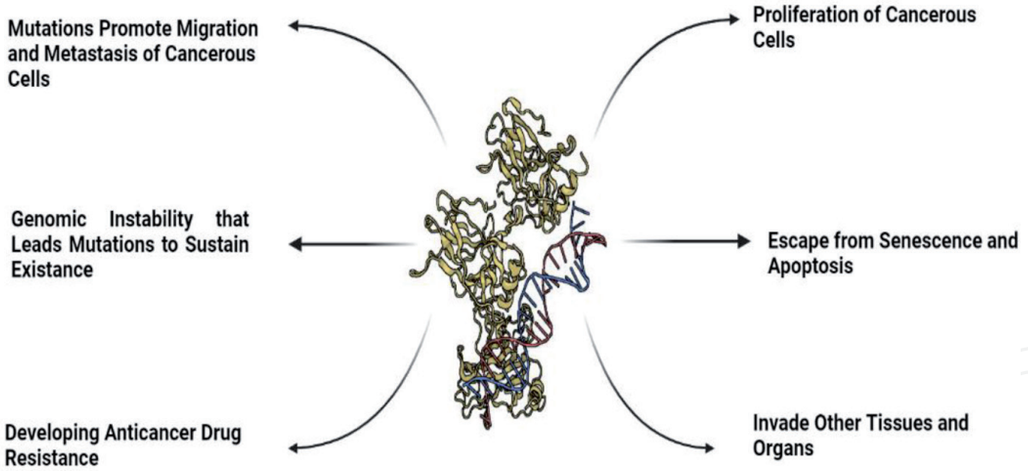

Figure 3.
Roles of p53 in cancerous cells.

and its partner proteins like its negative regulator MDM2 are of further interest for this purpose. This protein-protein interaction features specific properties for allosteric protein inhibition. Yet, the mutant composition of *p53* alters among distinct cancer types. As it is illustrated in **Figure 3**, *p53* follows various mechanisms in distinct cancer types.

Acknowledgements

Merve Nur AL, Berçem Yeman, and Kezban Ucar Ciftci acknowledge YOK 100/2000 Scholarship. Nazlican Yurekli acknowledges TUBITAK 2247-C Scholarship.

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References

[1] Xu Z, Wu W, Yan H, Hu Y, He Q, Luo P. Regulation of p53 stability as a therapeutic strategy for cancer. Biochemical Pharmacology. 2021; **185**:114407. DOI: 10.1016/j.bcp.2021.114407. Epub 2021 Jan 7

[2] Hoffman R, Benz EJ, Silberstein LE, Heslop H, Weitz JI, Anastasi J, et al. Hematology: Basic principles and practice. 2018. Available from: https://nls.ldls.org.uk/welcome.html?ark:/81055/vdc_100047773037.0x000001

[3] Demir Ö, Barros EP, Offutt TL, Rosenfeld M, Amaro RE. An integrated view of p53 dynamics, function, and reactivation. Current Opinion in Structural Biology. 2021;**67**:187-194. DOI: 10.1016/j.sbi.2020.11.005. Epub 2021 Jan 2

[4] Giacinti C, Giordano A. RB and cell cycle progression. Oncogene. 2006;**25**(38):5220-5227. DOI: 10.1038/sj.onc.1209615

[5] Kastan MB, Bartek J. Cell-cycle checkpoints and cancer. Nature. 2004;**432**(7015):316-323. DOI: 10.1038/nature03097

[6] Bargonetti J, Prives C. Gain-of-function mutant p53: History and speculation. Journal of Molecular Cell Biology. 2019;**11**(7):605-609. DOI: 10.1093/jmcb/mjz067

[7] Carroll JL, Michael Mathis J, Bell MC, Santoso JT. p53 adenovirus as gene therapy for ovarian cancer. Methods in Molecular Medicine. 2001;**39**:783-792. DOI: 10.1385/1-59259-071-3:783

[8] Lacroix M, Riscal R, Arena G, Linares LK, Le Cam L. Metabolic functions of the tumor suppressor p53: Implications in normal physiology, metabolic disorders, and cancer. Molecular Metabolism. 2020;**33**:2-22. DOI: 10.1016/j.molmet.2019.10.002. Epub 2019 Oct 18

[9] Yamasaki L. Role of the RB tumor suppressor in cancer. Cancer Treatment and Research. 2003;**115**:209-239. DOI: 10.1007/0-306-48158-8_9

[10] Hu J, Cao J, Topatana W, Juengpanich S, Li S, Zhang B, et al. Targeting mutant p53 for cancer therapy: Direct and indirect strategies. Journal of Hematology & Oncology. 2021;**14**(1):157. DOI: 10.1186/s13045-021-01169-0

[11] Biasoli D, Kahn SA, Cornélio TA, Furtado M, Campanati L, Chneiweiss H, et al. Retinoblastoma protein regulates the crosstalk between autophagy and apoptosis, and favors glioblastoma resistance to etoposide. Cell Death & Disease. 2013;**4**(8):e767. DOI: 10.1038/cddis.2013.283

[12] Zhang T, Hu H, Yan G, Wu T, Liu S, Chen W, et al. Long non-coding RNA and breast cancer. Technology in Cancer Research & Treatment. 2019;**18**:1533033819843889. DOI: 10.1177/1533033819843889

[13] Bertheau P, Lehmann-Che J, Varna M, Dumay A, Poirot B, Porcher R, et al. p53 in breast cancer subtypes and new insights into response to chemotherapy. Breast. 2013;**22**(Suppl. 2):S27-S29. DOI: 10.1016/j.breast.2013.07.005

[14] Bronner SM, Merrick KA, Murray J, Salphati L, Moffat JG, Pang J, et al. Design of a brain-penetrant CDK4/6 inhibitor for glioblastoma. Bioorganic & Medicinal Chemistry Letters. 2019;**29**(16):2294-2301. DOI: 10.1016/j.bmcl.2019.06.021 Epub 2019 Jun 26

[15] Januškevičienė I, Petrikaitė V. Heterogeneity of breast cancer: The importance of interaction between different tumor cell populations.

Life Sciences. 2019;**239**:117009. DOI: 10.1016/j.lfs.2019.117009. Epub 2019 Oct 24

[16] Dittmer J. Breast cancer stem cells: Features, key drivers and treatment options. Seminars in Cancer Biology. 2018;**53**:59-74. DOI: 10.1016/j.semcancer.2018.07.007. Epub 2018 Jul 27

[17] Kast K, Link T, Friedrich K, Petzold A, Niedostatek A, Schoffer O, et al. Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Research and Treatment. 2015;**150**(3):621-629. DOI: 10.1007/s10549-015-3341-3. Epub 2015 Mar 18

[18] Bellazzo A, Sicari D, Valentino E, Del Sal G, Collavin L. Complexes formed by mutant p53 and their roles in breast cancer. Breast Cancer. 2018; **10**:101-112. DOI: 10.2147/BCTT.S145826

[19] Prabhu KS, Raza A, Karedath T, Raza SS, Fathima H, Ahmed EI, et al. Non-coding RNAs as regulators and markers for targeting of breast cancer and cancer stem cells. Cancers (Basel). 2020;**12**(2):351. DOI: 10.3390/cancers12020351

[20] Abdeen SK, Aqeilan RI. Decoding the link between WWOX and p53 in aggressive breast cancer. Cell Cycle. 2019;**18**(11):1177-1186. DOI: 10.1080/15384101.2019.1616998. Epub 2019 May 16

[21] Gasco M, Shami S, Crook T. The p53 pathway in breast cancer. Breast Cancer Research. 2002;**4**(2):70-76. DOI: 10.1186/bcr426. Epub 2002 Feb 12

[22] Lim LY, Vidnovic N, Ellisen LW, Leong CO. Mutant p53 mediates survival of breast cancer cells. British Journal of Cancer. 2009;**101**(9):1606-1612. DOI: 10.1038/sj.bjc.6605335. Epub 2009 Sep 22

[23] Xiao G, Lundine D, Annor GK, Canar J, Ellison V, Polotskaia A, et al. Gain-of-function mutant p53 R273H Interacts with replicating DNA and PARP1 in breast cancer. Cancer Research. 2020;**80**(3):394-405. DOI: 10.1158/0008-5472.CAN-19-1036

[24] Zhang C, Liu J, Xu D, Zhang T, Hu W, Feng Z. Gain-of-function mutant p53 in cancer progression and therapy. Journal of Molecular Cell Biology. 2020;**12**(9):674-687. DOI: 10.1093/jmcb/mjaa040

[25] Synnott NC, O'Connell D, Crown J, Duffy MJ. COTI-2 reactivates mutant p53 and inhibits growth of triple-negative breast cancer cells. Breast Cancer Research and Treatment. 2020;**179**(1):47-56. DOI: 10.1007/s10549-019-05435-1. Epub 2019 Sep 19

[26] Janani SK, Dhanabal SP, Sureshkumar R, Surya NUS, Chenmala K. Guardian of genome on the tract: Wild type p53-mdm2 complex inhibition in healing the breast cancer. Gene. 2021;**786**:145616. DOI: 10.1016/j.gene.2021.145616. Epub 2021 Apr 1

[27] Srivastava P, Jaiswal PK, Singh V, Mittal RD. Role of p53 gene polymorphism and bladder cancer predisposition in northern India. Cancer Biomarkers. 2011;**8**:21-28. DOI: 10.3233/DMA-2011-0816

[28] Hollstein M, Rice K, Greenblatt MS, Soussi T, Fuchs R, Sørlie T, et al. Database of p53 gene somatic mutations in human tumors and cell lines. Nucleic Acids Research. 1994;**22**(17):3551-3555

[29] DeWolf WC. p53: An important key to understanding urologic cancer. AUA Update Series. 1995;**15**:258

[30] Solomon JP, Hansel DE. The emerging molecular landscape of urothelial carcinoma. Surgical Pathology Clinics. 2016;**9**(3):391-404. DOI: 10.1016/j.path.2016.04.004

[31] Kastenhuber ER, Lowe SW. Putting p53 in context. Cell. 2017;**170**(6):1062-1078. DOI: 10.1016/j.cell.2017.08.028

[32] Mansor SF. Manipulation of p53 protein in bladder cancer treatment. IIUM Medical Journal Malaysia. Jan 2021;**20**(1). DOI: 10.31436/imjm.v20i1.1764

[33] Knowles MA, Hurst CD. Molecular biology of bladder cancer: New insights into pathogenesis and clinical diversity. Nature Reviews Cancer. 2015;**15**(1):25

[34] Katkoori V, Jia X, Shanmugam C. Prognostic significance of p53 Codon 72 polymorphism differs with race in colorectal adenocarcinoma. Clinical Cancer Research. 2009;**15**:2406-2416

[35] Berggren P, Steineck G, Adolfsson J, Hansson J, Jansson O, Larsson P, et al. p53 mutations in urinary bladder cancer. British Journal of Cancer. 2001;**84**(11):1505-1511

[36] Thomas M, Kalita A, Labrecque S, Pim D, Banks L, Matlashewski G. Two polymorphic variants of wild-type p53 differ biochemically and biologically. Molecular and Cellular Biology. 1999;**19**(2);1092-1100. DOI: 10.1128/MCB.19.2.1092

[37] Chen W, Tsai F, Wu J, Wu H, Lu H, Li C. Distributions of p53 codon 72 polymorphism in bladder cancer—proline form is prominent in invasive tumor. Urological Research. 2000; **28**(5):293-296

[38] Soulitzis N, Sourvinos G, Dokianakis D, Spandidos D. p53 codon 72 polymorphism and its association with bladder cancer. Cancer Letters. 2002;**179**:175-183

[39] Kuroda Y, Tsukino H, Nakao H, Imai H, Katoh T. p53 codon 72 polymorphism and urothelial cancer risk. Cancer Letters. 2003;**189**:77-83

[40] Whibley C, Pharoah P, Hollstein M. p53 polymorphisms: Cancer implications. Nature Reviews Cancer. 2009;**9**:95-107

[41] Schulz W. Molecular Biology of Human Cancers. Netherlands: Springer; 2007

[42] Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. Lancet. 2018;**392**(10145):432-446. DOI: 10.1016/S0140-6736(18)30990-5. Epub 2018 Jul 27

[43] Vargo MM. Brain tumors and metastases. Physical Medicine and Rehabilitation Clinics of North America. 2017;**28**(1):115-141. DOI: 10.1016/j.pmr.2016.08.005

[44] Checler F, Alves da Costa C. p53 in neurodegenerative diseases and brain cancers. Pharmacology & Therapeutics. 2014;**142**(1):99-113. DOI: 10.1016/j.pharmthera.2013.11.009. Epub 2013 Nov 25

[45] Ham SW, Jeon HY, Jin X, Kim EJ, Kim JK, Shin YJ, et al. TP53 gain-of-function mutation promotes inflammation in glioblastoma. Cell Death and Differentiation. 2019;**26**(3): 409-425. DOI: 10.1038/s41418-018-0126-3. Epub 2018 May 21

[46] Lah TT, Novak M, Breznik B. Brain malignancies: Glioblastoma and brain metastases. Seminars in Cancer Biology. 2020;**60**:262-273. DOI: 10.1016/j.semcancer.2019.10.010. Epub 2019 Oct 22

[47] Agostini M, Melino G, Bernassola F. The p53 family in brain disease. Antioxidants & Redox Signaling. 2018;**29**(1):1-14. DOI: 10.1089/ars.2017.7302. Epub 2017 Nov 27

[48] Hooper C, Meimaridou E, Tavassoli M, Melino G, Lovestone S, Killick R. p53 is upregulated in Alzheimer's disease and induces tau phosphorylation in HEK293a cells. Neuroscience Letters. 2007;**418**(1):34-37. DOI: 10.1016/j.neulet.2007.03.026. Epub 2007 Mar 15

[49] LaFerla FM, Hall CK, Ngo L, Jay G. Extracellular deposition of beta-amyloid upon p53-dependent neuronal cell death in transgenic mice. The Journal of Clinical Investigation. 1996;**98**(7):1626-1632. DOI: 10.1172/JCI118957

[50] Xiong Y, Zhang Y, Xiong S, Williams-Villalobo AE. A glance of p53 functions in brain development, neural stem cells, and brain cancer. Biology (Basel). 2020;**9**(9):285. DOI: 10.3390/biology9090285

[51] Armstrong JF, Kaufman MH, Harrison DJ, Clarke AR. High-frequency developmental abnormalities in p53-deficient mice. Current Biology. 1995;**5**(8):931-936. DOI: 10.1016/s0960-9822(95)00183-7

[52] Pedrote MM, Motta MF, Ferretti GDS, Norberto DR, Spohr TCLS, Lima FRS, et al. Oncogenic gain of function in glioblastoma is linked to mutant p53 amyloid oligomers. iScience. 2020;**23**(2):100820. DOI: 10.1016/j.isci.2020.100820. Epub 2020 Jan 8

[53] Guo CF, Zhuang Y, Chen Y, Chen S, Peng H, Zhou S. Significance of tumor protein p53 mutation in cellular process and drug selection in brain lower grade (WHO grades II and III) glioma. Biomarkers in Medicine. 2020;**14**(12):1139-1150. DOI: 10.2217/bmm-2020-0331 Epub 2020 Jul 15

[54] 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 Discovery. 2020;**6**:53. DOI: 10.1038/s41420-020-0287-y

[55] Fang SS, Guo JC, Zhang JH, Liu JN, Hong S, Yu B, et al. A P53-related microRNA model for predicting the prognosis of hepatocellular carcinoma patients. Journal of Cellular Physiology. 2020;**235**(4):3569-3578. DOI: 10.1002/jcp.29245. Epub 2019 Sep 25

[56] Caruso S, O'Brien DR, Cleary SP, Roberts LR, Zucman-Rossi J. Genetics of hepatocellular carcinoma: Approaches to explore molecular diversity. Hepatology. 2021;**73**(Suppl. 1):14-26. DOI: 10.1002/hep.31394. Epub 2020 Dec 8

[57] Ozaki T, Nakagawara A. Role of p53 in cell death and human cancers. Cancers (Basel). 2011;**3**(1):994-1013. DOI: 10.3390/cancers3010994

[58] Meng X, Franklin DA, Dong J, Zhang Y. MDM2-p53 pathway in hepatocellular carcinoma. Cancer Research. 2014;**74**(24):7161-7167. DOI: 10.1158/0008-5472.CAN-14-1446. Epub 2014 Dec 4

[59] Hussain SP, Schwank J, Staib F, Wang XW, Harris CC. TP53 mutations and hepatocellular carcinoma: Insights into the etiology and pathogenesis of liver cancer. Oncogene. 2007;**26**(15):2166-2176. DOI: 10.1038/sj.onc.1210279

[60] Kunst C, Haderer M, Heckel S, Schlosser S, Mueller M. The p53 family in hepatocellular carcinoma. Translational Cancer Research;**5**(6):632-638. DOI: 10.21037/tcr.2016.11.79

[61] 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. Briefings in Bioinformatics. 2021;**22**(3):bbaa164. DOI: 10.1093/bib/bbaa164

[62] Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. Cancer Treatment and Research. 2009;**152**:3-13. DOI: 10.1007/978-1-4419-0284-9_1

[63] Liu P, Wang M, Li L, Jin T. Correlation between osteosarcoma and the expression of WWOX and p53. Oncology Letters. 2017;**14**(4):4779-4783. DOI: 10.3892/ol.2017.6747. Epub 2017 Aug 10

[64] Overholtzer M, Rao PH, Favis R, Lu XY, Elowitz MB, Barany F, et al. The presence of p53 mutations in human osteosarcomas correlates with high levels of genomic instability. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**(20):11547-11552. DOI: 10.1073/pnas.1934852100. Epub 2003 Sep 12. Erratum in: Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**(24): 14511

[65] Chen Z, Guo J, Zhang K, Guo Y. TP53 mutations and survival in osteosarcoma patients: A meta-analysis of published data. Disease Markers. 2016;**2016**:4639575. DOI: 10.1155/2016/4639575. Epub 2016 Apr 27

[66] Chen X, Bahrami A, Pappo A. Recurrent somatic structural variations contribute to tumorigenesis in pediatric osteosarcoma. Cell Reports. 2014;**7**(1): 104-112. DOI: 10.1016/j.celrep.2014.03.003

[67] Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. Journal of Biomedicine & Biotechnology. 2011;**2011**:583929. DOI: 10.1155/2011/583929. Epub 2011 Jan 18

[68] 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. The European Respiratory Journal. 2001;**18**(4):705-719. DOI: 10.1183/09031936.01.00062201

[69] Sameshima Y, Matsuno Y, Hirohashi S, Shimosato Y, Mizoguchi H, Sugimura T, et al. Alterations of the p53 gene are common and critical events for the maintenance of malignant phenotypes in small-cell lung carcinoma. Oncogene. 1992;**7**(3): 451-457

[70] Tammemagi MC, McLaughlin JR, Bull SB. Meta-analyses of p53 tumor suppressor gene alterations and clinicopathological features in resected lung cancers. Cancer Epidemiology, Biomarkers & Prevention. 1999;**8**(7): 625-634

[71] Chang YL, Wu CT, Shih JY, Lee YC. Comparison of p53 and epidermal growth factor receptor gene status between primary tumors and lymph node metastases in non-small cell lung cancers. Annals of Surgical Oncology. 2011;**18**(2):543-550. DOI: 10.1245/s10434-010-1295-6. Epub 2010 Sep 2

[72] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA: A Cancer Journal for Clinicians. 2005;**55**(2):74-108. DOI: 10.3322/canjclin.55.2.74

[73] Hainaut P, Pfeifer GP. Patterns of p53 G→T transversions in lung cancers reflect the primary mutagenic signature of DNA-damage by tobacco smoke. Carcinogenesis. 2001;**22**(3):367-374. DOI: 10.1093/carcin/22.3.367

[74] Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene. 2002;**21**(48):7435-7451. DOI: 10.1038/sj.onc.1205803

[75] Denissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. Science. 1996;**274**(5286):430-432. DOI: 10.1126/science.274.5286.430

[76] Smith LE, Denissenko MF, Bennett WP, Li H, Amin S, Tang M, et al. Targeting of lung cancer mutational hotspots by polycyclic aromatic hydrocarbons. Journal of the National Cancer Institute. 2000;**92**(10):803-811. DOI: 10.1093/jnci/92.10.803

[77] Kondo K, Tsuzuki H, Sasa M, Sumitomo M, Uyama T, Monden Y. A

dose-response relationship between the frequency of p53 mutations and tobacco consumption in lung cancer patients. Journal of Surgical Oncology. 1996;**61**(1):20-26. DOI: 10.1002/(SICI)1096-9098(199601)61:1<20::AID-JSO6>3.0.CO;2-U

[78] Gow CH, Chang YL, Hsu YC, Tsai MF, Wu CT, Yu CJ, et al. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Annals of Oncology. 2009;**20**(4):696-702. DOI: 10.1093/annonc/mdn679. Epub 2008 Dec 16

[79] Vogt U, Zaczek A, Klinke F, Granetzny A, Bielawski K, Falkiewicz B. p53 Gene status in relation to ex vivo chemosensitivity of non-small cell lung cancer. Journal of Cancer Research and Clinical Oncology. 2002;**128**(3):141-147. DOI: 10.1007/s00432-001-0305-2. Epub 2002 Jan 26

[80] Leslie WT, Bonomi PD. Novel treatments in non-small cell lung cancer. Hematology/Oncology Clinics of North America. 2004;**18**(1):245-267. DOI: 10.1016/s0889-8588(03)00146-1

[81] Swisher SG, Roth JA, Nemunaitis J. Adenovirus-mediated p53 gene transfer in advanced non-small-cell lung cancer. Journal of the National Cancer Institute. 1999;**91**(9):763-771. DOI: 10.1093/jnci/91.9.763

[82] Issaeva N, Bozko P, Enge M, Protopopova M, Verhoef LG, Masucci M, et al. Small molecule RITA binds to p53, blocks p53-HDM-2 interaction and activates p53 function in tumors. Nature Medicine. 2004;**10**(12):1321-1328. DOI: 10.1038/nm1146. Epub 2004 Nov 21

[83] Selivanova G, Wiman KG. Reactivation of mutant p53: Molecular mechanisms and therapeutic potential. Oncogene. 2007;**26**(15):2243-2254. DOI: 10.1038/sj.onc.1210295

[84] Magrini R, Russo D, Ottaggio L, Fronza G, Inga A, Menichini P. PRIMA-1 synergizes with adriamycin to induce cell death in non-small cell lung cancer cells. Journal of Cellular Biochemistry. 2008;**104**(6):2363-2373. DOI: 10.1002/jcb.21794