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Review

A Narrative Review of the TP53 and Its Product the p53 Protein

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Abstract

The main purpose of this paper was to generate a narrative review related to the current knowledge of the *TP53* gene and its product, the p53 protein. It was also attempted to elucidate the different p53 reactivation strategies of great interest, as various small molecules are being studied to reactivate mutant p53. PubMed and ScienceDirect were searched for p53, mutant p53, and wild-type p53 limited by the title filter through the end of 2022. The collected articles were studied, evaluated and summarized. In the short (p) arm of chromosome 17, there is a special place for *TP53*. (17p.13.1). It is made up of 19,180 bp, which includes thirteen exons, (elevem exons, two alternative exons), and ten introns. *TP53* is mutated in most types of human cancers resulting in aggressive cancer proliferation, immune system evasion, genomic instability, invasion, and metastasis. Under stress-free conditions, p53 function is negatively regulated by *HDM2,* a p53 target gene, which binds to it and establishes an auto-regulatory negative feedback loop that promotes proteasomal-dependent degradation. In these conditions, p53 maintains at low levels and normalizes biological operations as the master regulator of cell fate. However, under conditions of stress such as DNA damage, hypoxia, oxidative stress, oncogene expression, nutrient deprivation, ribosomal dysfunction, or telomere attrition the p53 selection pathway will be cell type-specific and depend on the type and severity of the cell damage. Post-translational

modifications such as phosphorylation and acetylation, which induce the expression of p53 target genes, contribute to the p53 selection pathway. In these conditions, p53 tetramerized and stabilized in the nucleus and activated, and its levels increased in the cell due to blocking the interaction with *MDM2.* Valuable findings have been discovered that elucidate the biological, biochemical, immunological, physiological, and pathological roles of p53 and its fundamental roles in cancer biology and genetics. The information gathered here should contribute to a better understanding of the impact of p53 deregulation on cancer and new research aimed at finding new anticancer strategies capable of reactivating the cancer suppressive function of WT and/or blocking the function of mutant p53 in order to improve cancer therapy and prognosis.

Keywords
p53; small molecules reactivate mutant p53; personalized medicine

1. Introduction

Humans have deoxyribonucleic acid (DNA) in their cells' nuclei which hold hereditary information [1]. The information in the DNA gives cells instructions for making proteins. Proteins drive important body roles, like constructing cells, digesting foods, and making up and moving the muscles. Each gene is a piece of deoxyribonucleic acid that holds a genetic map with total details and is passed on from parents to the next generation, creating traits similar to those of parents in children. Genes have nucleotide codes or sequences which provide information on the production of various RNAs and proteins to other cellular devices. To do this, cellular enzymes transcribe genes to form functional RNAs or produce mRNAs to translate into proteins. A few genes act as guides to making proteins. However, several of them are not coded for making these molecules. Human genes vary in size from a few hundred DNA bases to more than two million bases, and their total number is not fully known because the function of several transcripts remains indefinite such as non-protein-coding DNA. The number of genes that encode proteins is identified better but there are still on the orders of one thousand four hundred genes. Their coding potential has typically been disregarded, to some extent because of the difficulty in determining whether these sequences are translated. They called short open reading frames [2]. Humans have nearly 20,000-25,000 genes [3]. Their size ranges from 1,100 to 41,000 open pairs (1.1 to 41 Kb) [4]. Most genes are the same in all humans, but less than 1% are a little dissimilar between humans. Alleles are shapes of similar genes with minor alterations in DNA sequences. These minor alterations contribute to the unique physical characteristics of each individual. Scientists name them to track genes [5]. Because the names of the genes were long, they were given symbols that were a short combination of letters that abbreviated the names of the genes (and sometimes numbers). For example, *TP53* stands for tumor protein p53 exists in the p arm of chromosome number 17 (17p13.1) [6, 7] in humans. The product of this gene is also known by other names such as Li-Fraumeni syndrome, tumor suppressor p53, P53_HUMAN, and transformation-related protein 53. Yet it turns out to be the most investigated gene in human tumors. It was not appropriately understood after its early discovery which might clarify why it took quite a few decades after the 1979 description of the protein for the gene to rise

to the top spot in the literature. It is a transcription factor and suppressor tumor that responds to cell changes and induces apoptosis and DNA repair. In cancer cells, mutations in *TP53* lead to changes in the lower and upper-related pathways and changes in signaling. Loss of *TP53* function may be critical for cells, a point of contention in cancer development. The gene's importance is linked to its clinical value [8] because the detection of its mutant form in the patient's DNA, or its auto antibodies in serum would contribute to primary analysis of cancer types in which its mutation happens at a primary stage of cancer progression. Trials in the coming years of p53 research will be to deepen our understanding of p53 at the cellular level and translate this achievement into precision medicine. Although the first agents targeting p53 are used for some patients, a better understanding of the roles and functions of both wild type (WT) and mutant will likely pave the way for personalized treatments.

The present paper aimed to gather evidence from the current investigations and studies supporting the context-dependency of *TP53* and its product p53 protein in both wild-type and mutant perspectives. It was done to collect any cellular activity that p53 may have under stress and non-stress cell conditions to find information and evidence related to the gene. PubMed and ScienceDirect databases were searched for p53, mutant p53 and WT p53 which were limited by the title and English language filters. From the retrieved relevant studies, the information related to the *TP53* and p53 functions and their responsibilities in cells, and the molecular mechanisms of p53 affecting cell biology was summarized as follows.

2. TP53

2.1 History

Examinations of the cells containing integrated SV40 DNA called SV40 transformed cells revealed that a protein with 55 kDa weight was precipitated with the large T antigen. Peter Chumakov was the first scientist who cloned *TP53* from a mouse in 1982 [9]. One year later a cDNA library was created from sucrose-gradient-fractionated mRNA from SVT2, a mouse cell, by Oren and Levine [10]. In the same year overproduction of p53 was detected in cells transformed by a wide range of agents, spontaneous transformants, and embryonic carcinoma cells [11]. In 1984 TP53 was cloned [7]; its full length was subsequently cloned in 1985 [12]. At first, it was assumed that it was an oncogene due to the use of mutated cDNA following the purification of tumor4-cell mRNA [13-15]. But later it became a tumor suppressor gene [16, 17]. Oncogenes allude to the genes that alterations cause gain-of-function (GOF) effects, while tumor suppressor genes cause loss-of-function (LOF) effects that contribute to the cancer phenotype. Warren Maltzman and his colleagues were the first group demonstrating that *TP53* responds to DNA damage when exposed to Ultra Violet light [18]. In 1993, Michael Kastan found it an important controller at G1 arrest after DNA damage [19]. Scientists believe this gene is responsible as the "guardian of the genome in the nucleus and mitochondrial genetic content" [20-22]. The fourth decade of p53-related research saw TP53-based medications for cancer chemotherapy.

p53 acts as a tumor suppressor or oncogenic. Mutations in the *TP53* stimulate cell growth and tumor progression. But an investigation revealed that p53 could promote cancer growth by increasing the metabolism of hepatocellular carcinoma cells [23]. p53 transcription triggers PUMA expression, which further initiates apoptosis. But certain levels of PUMA protein interfere with normal mitochondrial function, leading to a shift in mitochondrial energy metabolism from oxidative

phosphorylation to glycolysis [23]. Because p53-dependent cell cycle arrest is not mandatory for p53-dependent cancer suppression, p53-dependent apoptosis appears necessary for p53-dependent cancer suppression. PUMA-deficient mice, in which p53-dependent apoptosis is blocked are not cancer-prone. In contrast, PUMA is overexpressed in many human cancers and loss of PUMA reduces tumorigenesis in certain mouse models, suggesting that it could act as an oncogene. Furthermore, p53 R172P mutant knock-in mice, completely defective in p53-dependent apoptosis, are not susceptible to cancer. Knock-in mice were defective in p53-dependent apoptosis, cell cycle arrest, and senescence did not increase the frequency of spontaneous tumorigenesis. Knocked out *MDM2* in hepatocyte-specific KRAS G12D mutant mice revealed that p53 accumulation happened in mouse hepatocytes [24]. These p53-activated mice exhibited increased inflammatory responses, hepatocyte apoptosis, and senescence-associated secretory phenotype, facilitating a carcinogenic microenvironment [24, 25]. Hepatic progenitor cells from p53-accumulating mice were injected into experimental mice growing tumors. The development of hepatocellular carcinoma and other related phenotypes no longer happened after the knockdown of *TP53*, signifying that p53-accumulated mice promote the development of hepatocellular carcinoma [24]. Cellular activities regulated by p53 are integrated into cancer suppressive roles, but p53-induced regulation of certain elements might also provide a survival advantage for cancers.

2.2 Structure

TP53 consists of 11 typical plus 2 atypical exons and 10 introns (as shown in Figure 1). It spans nearly twenty kilobytes (20 kb), and its non-coding exon 1 is isolated from the remains of the coding sequence by an extremely conserved intron that covers more than half of the gene. The non-coding exon 1 is the part that could form a stable stem-loop assembly that binds strongly to WT but not to its mutant form. The coding sequence comprises 5 districts that show a high degree of conservation in vertebrates, largely in five exons (exon 2 and exons 5-8). However, invertebrate sequences display little similarity to vertebrate *TP53* [26, 27]. Exon 1 and most of Exon 11 are non-encrypted. They are not encoded in mRNA, whereas the hotspot gene is located on exons 5-8. More than 90% of mutations occur in these exons.

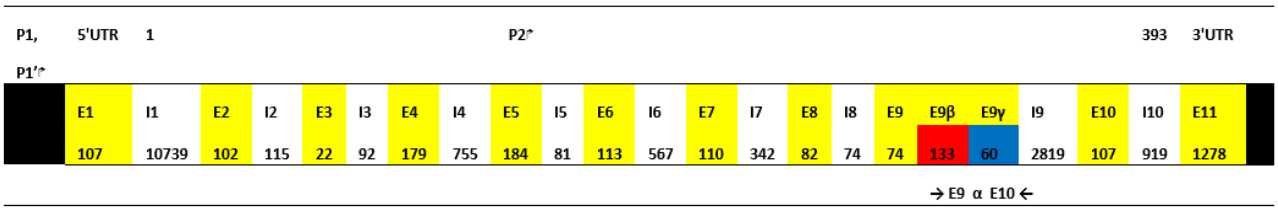

Figure 1 Human *TP53* Boxed structural organization. Alternative promoters (P1, P1' and P2) and alternative splicing (α, β, γ) are designated. Classical exons 1 to 11 are shown in yellow and introns in white columns. E2 to E11 are translated into a full-length p53 (Promoter 1, 393 residues). E9β (yellow-red) and E9γ (yellow-blue) are used via alternate splicing resulting in unlike transcriptions. E1 and E11 attached to black boxes are noncoding sequences; E2 to E11 are coding sequences. The connection between E9 to E10 is showing *TP53* α. P1, P1', and P2 are designated as ↱. The size of the boxes is not proportional to the size of the exons. The *TP53* spans a region of 19,054 base pairs. Exons β and γ contain STOP codons and result in truncated proteins missing part of the

carboxy terminus of the protein. Translation of exons 9β & 9γ adds 10 and 15 residues, respectively. Two isolate sites are able to initiate *TP53* transcription in normal tissues. They are upstream of exon 1 and from an internal promoter positioned in intron 4. The alternative promoter results in the expression of a truncated N-terminal p53 protein located at codon 133. Intron-9 can be alternatively spliced to generate p53, p53β, and p53γ. Thus, *TP53* is capable of encoding at least nine non-identical isoforms. Six of them, p53, p53β, p53γ, Δ133p53, Δ133p53β and, Δ133p53γ, are as a result of alternative splicing of the intron-9 and usage of the alternative promoter in intron-4. The other three, Δ40p53, Δ40p53β, and Δ40p53γ, are as a result of alternative splicing of introns -9 and -2, alternative promoter usage, and alternative initiation of translation [28]. Thus, human *TP53* differentially expresses in normal tissue at least nine mRNAs in a tissue-dependent manner. In addition, the tissue-specific expression of p53 isoforms can elucidate the tissue-specific regulation of p53 transcriptional function in response to hypoxia, pH, UV light, and γ-irradiation. So, liver activates p21 and cell cycle arrest in a p53-dependent manner, but thymus and spleen induce massive p53-dependent apoptosis in reply to an equal amount of γ-irradiation [29-31].

2.3 Mutation

Cancers with mutations in the *TP53* have been reported [32, 33]. They are adrenocortical, bladder, breast, brain, colorectal, cholangiocarcinoma, head and neck, liver, leukemia, lung, lymphoma, osteosarcoma, melanoma, myosarcoma and, ovarian cancers. Results from the Pan-Cancer cohort showed that 42% of cases had shown mutations in their *TP53*. Basal subtype breast cancers also accompanied *TP53* mutations. During cancer formation, a *TP53* mutation, either inherited or sporadic, is normally followed by loss of heterozygosity, which ends in complete p53 deficiency. *TP53* mutations are categorized into the DBD, Zinc-binding, and destabilizing assembly. The mutations would be appeared in all coding exons, with superiority in exons 4-9, which encodes the DBD. Of the mutations in the DBD, about 30% occur in G245, R175, R248, R249, R273, and R282 residues. They are replicated in somatic cells in almost every type of cancer [34]. These hotspot residues could be explained by the sensitivity of specific codons to carcinogen-induced changes and by the positive selection of mutations that endow the cell with growth and survival advantages. Most of these mutations impede the protein's ability to bind to target DNA, so the gene will not be edited. However, according to the mutation sites, p53 mutations are classified into class I and II. Class I is a type of DNA contact in which a mutation occurs in amino acids that directly bind to p53-responsive elements in DNA to disrupt the sequence-specific DNA binding activity of p53 without big changes in protein structure. While class II is a conformational or structural variant in which a mutation results in a big change in p53 conformation leading to loss of DNA binding activity. However, not all p53 mutants lose DNA binding activity. Interestingly, mutant p53 not only loses the tumor suppressor functions of WT p53, but also induces cancer progression, chemoresistance, and metastasis independent of WT p53, termed GOF. Mechanisms of GOF are mainly caused by the binding of misfolded p53 with tumor suppressors (e.g., p63, p73, MRN complex) to inhibit their function or with oncoproteins (e.g., ETS2, SREBP2, VDR, NF-Y) to enhance their function. Increasing evidence suggests that the accumulation of mutant p53 protein is critical for oncogenic GOF activities. Increased mutant p53 levels by MDM2 depletion and genotoxic stress enhance GOF

activities including cancer metastasis. While mutant p53 is stabilized or degraded by mechanisms similar to WT p53, several reports suggest distinct mechanisms of stabilization or degradation of mutant p53 from those of WT p53. In cancer patients, at codon position 72, a shared polymorphism participates in replacing an arginine for a proline [35]. A genetic correlation between this difference and cancer susceptibility has been identified. However, the results have been provocative. For example, one meta-analysis failed to find an association between cervical cancer and susceptibility [36]. Sonoyama and his colleagues concluded that the *TP53* proline mutation had considerably affected pancreatic cancer risk among men [37]. Another study whose participants were Arab women who had breast cancer concluded that at codon 72, proline homozygosity was a reduced risk factor [38]. Another study concluded that the three polymorphisms in codon 72, MDM2 SNP 309, and A2164G might be related to non-oropharyngeal cancer susceptibility and that MDM2 SNP 309 combined with a mutation at codon 72 might be involved in the process of facing cancer in women [39]. Two additional studies stated that polymorphism in codon 72 was associated with an increased risk of lung cancer in men [40, 41]. Against these conclusions polymorphism at codon 72 could not clarify the risk of getting cancer among adenocarcinoma cases and non-smokers [42]. Also no acceptable link between polymorphism at codon 72 and leukemia susceptibility was found [43]. Two studies concluded that no remarkable risk existed between codon 72 polymorphisms in both colorectal [44] and endometrial cancer patients [45]. A birth cohort study found an association between non-mutated *TP53* arginine and individuals without a family history of cancer [46]. Another study concluded that *TP53* homozygous (Prolin/Prolin) genotype was linked with an augmented risk for renal cell carcinoma [47]. Most mutations occurring in the DBD abolish the function of p53 to bind to target DNA genes. Therefore, it inhibits the transcriptional activation of these genes. Thus, mutations in the DBD are loss-of-function recessive mutations that result in a less active or inactive form of the protein, whereas gain-of-function (GOF) mutations result in a more active form of p53 or the acquisition of a different activity. Numerous p53 missense mutations possess GOF activities.

p53 with mutations in OD dimerizes with WT, preventing them from active transcription. Hence, mutations in this region show a dominant-negative result on p53 activity. To date all mutations related to the *TP53* are gathered in the IARC *TP53* Database [48].

During cancer development, most of the *TP53* mutation, either sporadic or inherited, is missense. It is mutated in nearly half of NSCL and colon cancers, and 30% of breast cancers. Oddly, it is found that WT *TP53* is deactivated in nearly 90% of melanoma cases with around 10% carrying disabling point mutations. However, this quantity could be as high as 19%. In other words, wild-type p53 in melanoma patients is unable to function like a suppressor factor. With the current understanding of the complexity of *TP53* deactivation and the preclinical achievements in *TP53* reactivation in melanoma, a p53-based therapy may become possible by reactivating the *TP53* normal functions. Targeting the transcriptional cofactor inhibitor member of the p53 family of apoptosis-inducing proteins has provided a promising opportunity for melanoma patients. However, its regulation of binding partners, *p63* and *p73*, seems to require fundamental investigations. Given these efforts, it is anticipated that modulation of the inhibitor of apoptosis-inducing p53 family only effective against wtp53-expressing cancers may be an effective approach to restore *TP53* function in melanomas that express WT p53. Restoration of the tumor suppressor function of p53 is an opportunity for a similar therapeutic tactic with BRAF V600E to achieve the best efficacy in melanoma. Almost half of melanomas have to activate BRAF mutations. More than 90% of mutations in these patients are located in codon 600.

Allelic loss, deletions, and rearrangements of *TP53* happen as well. *TP53* could be inactivated by various single-point mutations unlike *RAS* genes, which have a few mutational codons. Now, it is accepted that the *TP53* different mutations in cancers can help to identify the exact carcinogen that is genotoxic. In other words, different carcinogens cause different "unique mutations" in the gene. Some of them reflect endogenous oxidative damage, but the appearance of mutations in the gene in liver cancers from individuals exposed to aflatoxins suggests the appearance of mutations unique to aflatoxin. In places where humans are exposed to more sunlight and therefore the probability of getting skin cancer is higher, the mutations in *TP53* in these cancers are typical of pyrimidine dimers caused by UV light and finally the spectrum of mutations caused by (+)-benzo [a] is 7,8-pyrene. diol-9,10-epoxide-2 in cultured cells is similar to the spectrum of mutations in p53 in lung cancers from smokers.

Mutations in evolutionarily conserved codons are shared in many types of cancer. The appearance of p53 mutation varies between patients with esophageal, hematopoietic, and reticuloendothelial cancers. The transitions predominate in lymphoid tumors and the brain and colon, while the G:C to T:A translocation is the most common substitution seen in lung and liver cancer. Mutations in A:T base pairs are more common in esophageal than in other solid tumors. Mutations in CpG dinucleotide mutation hotspots cause most changes in brain and colorectal cancers, lymphoma and leukemia. G to T transversions is scattered between many codons in lung, breast, and esophageal cancers. Several studies demonstrated that in liver cancers in patients from geographical zones where both aflatoxin B1 and HBV were existing most mutations occurred in only one nucleotide pair of codon 249. In brief, a mutation in *TP53* results in various deleterious effects depending on many factors, such as mutation type and cell context. These effects can be summarized into: (a) loss of WT p53 functions, (b) dominant negative effects, and (c) GOF activities.

2.3.1 Germ Line Mutations

Frederick Pei Li and Joseph F. Fraumeni Jr. found families in which other members had a variety of cancers, mainly in their soft tissues, early brain and breast cancers, osteosarcoma and leukemia, and carcinomas of the adrenal cortex, lung, and pancreas in1969 [49]. Comparable comments were reported by Lynch in 1979 [50]. This autosomal dominant disease is named Li–Fraumeni syndrome [51]. A mutation found in codon 248 of *TP53* that resulted in a change of arginine CGG to TGG, tryptophan was responsible [52].

2.4 Mechanism of Function

TP53 is inactive in cells under normal conditions [53]. Loss of alleles and single-base alteration are the most kinds of *TP53* deactivation. These mutations can be obtained by cellular or viral proteins that are critical to exact cancer [54]. The gene plays a significant role as a regulatory factor in controlling growth in impaired cells [55]. When DNA damage is present in mammalian cells, p53 expression increases and p53 halts the cell cycle at the G1 phase by allowing time for the DNA-repair machinery If the DNA repair process is effective, the cell continues its cycle. Otherwise, the cell will undergo apoptosis.

2.4.1 Function after Mutation

The mutation impairs its tumor suppressor ability and exerts oncogenic GOF activities independently of WT. Mutant *TP53* GOF is mainly caused by its binding to other oncogenic or tumor suppressor proteins. Evidence suggests that the stabilization of mutant *TP53* is essential for its GOF ability. So far, little is known about the factors that alter the stability of mutant *TP53* and its oncogenic GOF activities. When the gene is damaged, its tumor-suppressing ability is severely compromised. Patients who inherit only one functional copy of this gene are more likely to develop cancers in early adulthood (Li-Fraumeni syndrome).

Most human cancers showed a deletion or mutation in *TP53* [56-76]. Loss of *TP53* function causes genomic instability, often leading to an aneuploid phenotype [77]. DNA sequencing helped to detect mutations in the gene. Single mutations can have a wide range of functional effects from mild to severe [78, 79]. The wide range of cancer phenotypes, as consequences of gene mutations, is also supported by the fact that different p53 isoforms implement diverse cellular mechanisms associated with cancer prevention. Therefore, the mutation can create diverse isoforms, prevent their overall function in different cellular mechanisms, and thus spread cancer phenotypes. Research has shown that p53 isoforms are differentially expressed in different human tissues, and loss-of-function or GOF mutations of p53 isoforms can cause tissue-specific cancer or cancer stem cell potential in different tissues [80-83]. Mutations in the II-V conserved regions at exon 4 (codons 129-146), exon 5 (codons 171-179), exon 7 (codons 234-260) and exon 8 (codons 270-287) have a significant effect. The protected amino acids glycine at position 245 and arginine at positions 175, 248, 249, 273 and 282 are more vulnerable. Mutations are mostly missense, resulting from base pair replacements, but some are deletions and insertions and have a dominant negative outcome. Research on knock-out mice showed normal development, but the mice quickly developed cancer.

2.5 Family

In 1979 two human genes similar to *TP53* were identified [84-86]. The *P63* and *P73* reside in 3q27-29, and 1p36.2-3 respectively. They were highly compatible especially in the DBD with *TP53* and can therefore activate *TP53* target genes [85]. These three genes form the *TP53* family. However, a study that each group of mice was knocked out in one of the genes in the *TP53* family showed that each member also had their specific target genes [87]. As a result, the important action of *P63* in development, especially skin development and its derivatives [88], and the action of *P73* in the olfactory system development have been identified [89].

Investigations show that all members of this family are documented in the form of many isoforms. Several isoforms, called trans-activations, that have both activating domains TAD1 and TAD2, promote differentiation and apoptosis and suppress cancer development. In contrast, N-delta isoforms (ΔNs), which do not have one or both activating domains, are involved in the proliferation of trans-activation types in cell proliferation [90]. An accurate balance between ΔNs and trans-activation isoforms is necessary to regulate the activity of trans-activation isoforms, and inappropriate and unbalanced expression of these isoforms may lead to tumor formation. In this regard, different studies have shown the inability to regulate the expression of ΔNs isoforms in cancer and their possible role in its development. Near 50% of all human cancers show mutation in *TP53*, and it appears that in the other half, changes in the up or down regulatory pathways of *TP53* are involved [86].

Like the *P63*, the *P73* could be transcribed from an alternative promoter in the intron 3. P73 expresses at least 7 alternatively spliced RD isoforms (α, β, γ, Δ, ε, ζ, η) and at least 4 alternatively spliced N-terminal isoforms with different TAD moieties. It expresses no less than 35 mRNA variants, which theoretically can encode 29 different isoforms of p73. The p73 isoforms encoded by exon-2 and/or exon-3 mRNA variants start at different ATGs. Hence, they contain different parts of the RD, signifying they may have diverse specific actions and protein interactions. The p73 isoforms can attach specifically to DNA by the p53 and p73Responsive Elements to induce transcription of target genes. Like p53, such induction could be ended with apoptosis or cell-cycle arrest [91, 92]. Experimental mice are functionally deficient for all p73 isoforms and show manifold defects, chronic infections, hippocampal dysgenesis, hydrocephalus, inflammation, and irregularities in pheromone sensory paths. However, they did not display any increase in vulnerability to cancer.

3. p53

3.1 Discovery

In 1979 six groups of scientists, who separately studied, identified a protein with 53 kDa weight from both human and mouse cells [93]. Studies of SV 40 virus-transformed cells confirmed that a 55 kDa protein is precipitated with the large T antigen [94-100]. This relationship was shown to be the result of an *in vivo* association between p53 and large T antigen [96]. It was then assumed that the cellular genome might be encoded by p53 [93]. It should be noted that no middle-T was found for SV virus 40 and that the molecular weight of p53 was similar to that of the polyoma middle-T antigen. In 1979, the 54 kDa protein was found to be expressed in a wide variety of SV virus 40 transformed cells and in uninfected embryonic cancer cells [97]. A partial peptide map of this 54 kDa protein was identical between diverse cell lines, but distinctly different from the peptide map of SV virus 40 large T antigen [95, 97]. It was then postulated that SV virus 40 infections or transformation of mouse cells excites the synthesis or stability of a cellular 54-kDa protein. Over the first decade of research, it was shown to have many diverse faces and activities. However, this was a result of the different *TP53* clones that were isolated. While several researchers studied mutant p53 clones identified as an oncogene, other groups focused on WT P53 clones identified as tumor suppressors [101, 102].

Now it has been passing nearly 15250 days [102]. A simple search in PubMed shows more or less every 4 hours one paper has been indexed in this database. This interest is peculiar to only one gene/protein. It shows its essential roles in regulating the number of cells and the frequency of p53 dysregulation in human diseases mainly in cancer. Indeed, the interest of 80,000 plus publications on the p53 gene/protein would not have happened this way. The reason for the focus on cancer in the p53 field was that all 4 exploratory papers were about cancers and viruses that cause cancer, and almost all of the scientists who were interested in, and therefore went into, the field was cancer biologists [101]. p53 is any protein isoform encoded by homologous genes in different organisms, for example, *Trp53* in mice and *TP53* in humans. The time of breakthrough findings achieved since p53 discovery has been summarized in Table 1.

Table 1 shows a time of breakthrough findings achieved since p53 discovery.

Cancer history paradigm	Year	p53 history
Viral Theory	<1979	
	1979	p53 Discovery
Oncogene	1981	
Activated *ras* in human cancer	1982	
	1983	Murine p53 cloning
Tumor suppressor gene	1984	p53 cooperates with *ras*
Rb cloning	1986	
	1989	1) p53 inactivated in human cancers 2) WT p53 is a growth suppressor
	1990	Germ line mutation in Li-Froumani family
	1994	p53 mutants can be oncogenic
Stem Cell Theory	1996	
Stem cell discovery	2000	
	2009	p53 regulate stem cell fate
	2012	Allele-specific p53 mutant reactivation
	2017	Small molecules reactivate mutant p53
CD19 CAR-T cell treatments	2018	
	2019	Functional ligand design for modulating mutant p53 aggregation

3.1.1 Human p53

Human p53 active structure is a tetrameric complex with 4 identical chains each consisting of 393 residues [103]. From the structural point of view, each subunit consists of 393 amino acids and 5 highly conserved regions. Residues 1-42 (TADI) and residues 43-62 (TADII) are essential for p53 regulation. Because they offer binding sites for the transcriptional machinery and MDM2, the negative regulator. Residues 102-292 (DBD) are pivotal for their transcriptional action of it. DBD contains 4 of the 5 conserved boxes in its structure. Residues 323-356 (OD) permit the protein to make a tetramer figure prearranged as a dimer of dimers [104].

3.2 Structure

TP53 encodes a DNA sequence-dependent transcription factor that maintains genome integrity by regulating apoptosis, cell cycle arrest, and cell senescence [105]. It encodes no less than 12 different protein isoforms due to alternative mRNA splicing, translation start sites, and promoter usage [80, 106, 107]. Also, it can either transactivate by attaching to specific DNA-responsive elements [108], or repressing transcription of promoters that do not comprise binding sequences. Its affinity, cooperativity and DNA binding specificity are strongly related to its structural topography. It is a nuclear phosphoprotein containing about 393 amino acids. It has 4 domains, including a highly charged acidic domain with about 75 to 80 residues, a hydrophobic proline-rich domain from positions 80 to 150, a central domain from 150 to 300, and a highly basic C-terminal domain [109] as shown in Figure 2.

Figure 2 Boxed Domain structure of human p53 protein.

WT p53 is a labile protein [110]. It has 7 domains. The transactivation domain (TAD) contains AD1 and AD2. The N-terminal domain contains AD1 and AD2, PRD, and multiple phosphorylation sites.

1- AD1: activation domain one. It activates transcription factors and make of from residues 1-42. AD1 has 2 complementary transcriptional activation domains. They are major (residues 1-42) and minor (residues 55-75) one precisely dealing with the ability to regulate many pro-apoptotic genes [111].
2- AD2: activation domain two. It is significant for apoptotic action, residues 43-63, and required for nuclear receptor signaling [112].
3- PRD: Proline rich domain. It is significant for p53 apoptotic action through nuclear exportation via mitogen-activated protein kinase, residues 64-92 [113, 114].
4- DBD: Central DNA-binding core domain. It has many arginine (residues 102-292) and one Zinc atom. It is in charge for binding the p53 co-repressor LIM domain only protein 3 [115].
5- NLS: Nuclear localization signaling domain. Residues from 316-325 [112].
6- OD: Homo-oligomerization domain. Residues from 307-355. Tetramerization is indispensable for the action of p53 *in vivo* [116-118].
7- RD: Regulation of DBD or C-terminal domain. It is involved in down regulation of DNA binding of the DBD [119]. Residues 56-393.

In addition, a tandem of 9-amino-acid transactivation domains (9aaTD) was documented in the AD1 and AD2 regions of transcription factor p53 [120]. Knockout mutations and position for p53 interaction with Transcription factor II D [121] are 9-amino-acid transactivation domains that mediate p53 interaction with general co-activators like replication protein A, CBP/p300 (all 4 domains), GCN5 and PC4, MDM2, and TAF9 [120, 122].

3.2.1 Molecular Weight

p53 is any isoform of a protein encoded by homologous genes in several creatures, such as *TP53* in humans and *Trp53* in mice. The name p53 was given in 1979. Sodium dodecyl sulfate-polyacrylamide gel analysis showed that it is a 53-kilodalton protein. However, the actual mass of the full-length p53 protein (p53α) based on the sum of masses of the amino acid residues, is only 43.7 kDa. High numbers of proline residues, in its structure, reason for this deference which slows its migration on sodium dodecyl sulfate-polyacrylamide gel electrophoresis, thus making it seem heavier than it is [123]. *TP53* encodes no less than 15 different isoforms, diverse in size from 3.5 to 43.7 kDa in human cells establishing the p53 protein isoforms [124].

3.3 Biology

WT p53 is a 393-amino-acid nuclear phosphoprotein. WT p53 performs an essential function in the DNA transcription process [125], cell growth [126], and proliferation [127] plus in a lot of metabolic paths [128-132] and the immune system [133, 134]. It suppresses uncharacteristic cell proliferation. Thus, it may represent a significant mode of function for protection against cancer development [135]. It also seems a significant player in apoptosis and autophagy [136]. When a mutation occurs, its product loses its ability to block irregular cell growth [137]. Some mutations generate a distinct type of p53 protein that fundamentally stimulates cell division and upsurges the risk of developing cancer [138, 139]. They are more aggressive, more apt to metastasize, and often fatal [137]. Surprisingly the gene can create 15 dissimilar isoforms resulting in 15 different proteins [140-144]. p53 bounds to DNA and is found in a small amount in the nucleus of cells without stress under normal conditions. It is localized in the nucleus, but higher amounts, even 5-100 times, can be easily detected in transformed cells in culture and cancerous cells. Unlike short-lived WT p53, which has a half-life of twenty minutes, mutant p53 has a long half-life of 2-12 hours. WT p53 is labile protein. After DNA damage p53 became more stable by post-translational modifications and its concentration in the nucleus increased dramatically [145]. In response to stress conditions, WT and mutant p53 accumulate in cells. But WT returns to basal level following recovery from stress; mutant form remains stable. Expression of considerable amounts of WT p53 has 2 consequences, apoptosis or cell cycle arrest. The reflection that DNA-damaging agents induce p53 levels in cells directed to the definition of p53 as a checkpoint element. While essential for survival, in respone to genotoxic insult, its role as an emergency brake, triggering cell cycle arrest or apoptosis to protect the DNA from accumulating additional mutations. Cells lacking p53 expression are unstable and more cancer-prone [146, 147].

3.4 Regulation

A series of post-translational modifications both during normal conditions and in stress-induced responses regulate p53. *TP53* is known to be activated in reply to external stressors such as H_2O_2 [148], non-ionizing radiation [18], ionizing radiation (gamma radiation), oxidative stress [149] osmotic shock, ribonucleotide depletion, hypoxia [150], and de-regulated oncogene expression. Two actions manifest this activation. First, the half-life of p53 increased, resulting in rapid accumulation in stressed cells. Second, a conformational change forces p53 to become active as a transcriptional regulator in these cells. Phosphorylation at RD domain is a critical event leading to p53 activation which can be assumed as the main target for transmitting protein kinase stress signals. The protein kinases that are known to target the RD domain can be roughly classified into 2 distinct collections. The first collection goes to the MAPK family, ERK1-2, JNK1-3 which is known to answer to many types of stress, such as membrane damage, oxidative stress, heat, cold and osmotic shock. The other is implicated in the genome integrity checkpoint, a molecular cascade that detects and responds to many types of DNA damage caused by genotoxic stress. This collection includes ATR, ATM, Chk1 and Chk2, DNA-PK, CAK, and TP53RK. Oncogenes similarly induce p53 activation mediated by the p14ARF vector. In unstressed cells, the amount of p53 is kept low by constant degradation. MDM2 (HDM2 in human), a product of p53, attaches to p53, stopping its function and moving it from the nucleus to the cytosol. Also, MDM2 acts as a ubiquitin ligase and covalently binds ubiquitin to p53, thus targeting p53 for proteasomal degradation. But p53 ubiquitylation is

rescindable. One of the first molecules that serve as an MDM2 inhibitor is Nutlin-3 [151]. Furthermore, MI-63, a novel molecule, binds to MDM2 and induces p53 action under conditions where p53 function is inhibited [152].

N-terminal phosphorylation of p53 by the protein above kinases causes loss of MDM2 binding. Pin1 then binds to p53 and induces a conformational change in p53, further inhibiting MDM2 binding. Phosphorylation also allows the binding of transcriptional activators such as p300 and p300/CBP, which then acetylate the RD and expose the DBD, allowing it to activate or repress specific genes. Deacetylase enzymes (Sirt1 & Sirt7) can deacetylate p53 and lead to the inhibition of apoptosis [153].

WT p53 acts by different mechanisms.

i) WT p53 can activate DNA repair pathways when DNA is in constant damage by generating special proteins. If the cell stays here long enough, the DNA repair proteins will have enough time to repair the DNA, allowing the cell to enter the cell cycle. In addition p21, a product of *WAF1/CIP1* attaches to the G1-S/CDK complexes inhibiting their action. p21 fixes the CDK complexes that drive forward the cell cycle and inhibit their kinase function, thereby arresting the cell cycle to let repair happen. It could also arbitrate differentiation-related growth arrest and a more permanent growth arrest associated with cellular senescence. When p21 is complex with CDK2, the cell cannot proceed to the next stage of cell division. In contrast, a mutant p53 no longer binds efficiently to DNA, so the p21 protein is unavailable to function as a "stop signal" for cell division [154]. Human embryonic stem cell studies often define a dysfunctional p53-p21 partnership of the G1/S checkpoint path with downstream relevance for cell cycle regulation and the DNA damage reply. Notably, p21 mRNA is upregulated in human embryonic stem cells following the DNA damage response, but p21 is undetectable. Activated p53 binds DNA and activates the expression of *miR-34a* [155]. In human embryonic stem cells, p53 activates several microRNAs (miR-302a, b, c, and d), directly inhibiting p21 expression in human embryonic stem cells [156]. So, it may play an important factor in aging [157].
ii) p53 can stop the growth by keeping the cell cycle at the G1/S regulation point upon detecting DNA damage.
iii) p53 can start apoptosis or autophagy when DNA damage verifies to be irrecoverable.

Recent investigations have linked the RB1 and p53 paths, via p14ARF, signifying that these paths might control each other [158].

WT and mutant p53 reply to DNA damage, hypoxia, metabolic, oxidative, and radiation stress. Their regulation happens at the transcriptional, post-transcriptional, and post-translational level. At the transcriptional level, WT attaches directly to p53 response elements whereas mutant p53 attaches to the other transcription factors. In other words, the mutation at the DBD prevents its binding to the DNA p53 response elements. WT and mutant p53 can regulate the expression of microRNAs and interact directly/indirectly with other proteins to induce a cellular response. WT p53 biological response is cancer suppression, but mutant p53 response is metastasis and chemo/radioresistance. Also, UV light can stimulate p53 expression, triggering damage to DNA and p53 recruits procedures resulting in tanning [159].

In 1909, Paul Ehrlich was the first scientist to hypothesize that the immune system could control cancerous growth, later called "immune surveillance" by Burnet and Thomas [160-162]. It has also been found that p53 can be regulated through cytokine signaling, consistent with the observation

that persistent inflammation makes stress which can perform a title role in cancer initiation and development [163].

3.5 Isoforms

TP53 encodes 12 isoform proteins including p53α, p53β, p53γ, Δ40p53α, Δ40p53β, Δ40p53γ, Δ133p53α, Δ133p53β, Δ133p53γ, Δ160p53α, Δ160p53β, and Δ160p53γ have been identified. The first one, p53α, is never expressed alone. The isoforms are expressed in a tissue-dependent manner [80]. We can distinguish the full-length p53 protein isoforms into different protein domains. Starting from TAD 1, and TAD 2, which are required to trigger a subset of p53 target genes. It is followed by PRD (PXXP), whereby the motif PXXP is repeated (P = Proline and X = any AA). This part is required for p53-mediated apoptosis [164]. These isoforms Δ133p53β, γ and Δ160p53α, β, γ are lack PXXP hence they cannot facilitate apoptosis, describing the different roles of the *TP53* gene [104]. The DBD enables the p53 proteins to sequence-specific binding. The carboxyl-terminal domain which includes NLS, NES and OD completes the p53 protein. The NLS and NES are in charge of p53 subcellular regulation. Through OD, p53 can procedure a tetramer assembly which can attach to DNA. Some domains may be lost between isoforms, but they all share most highly conserved DBD [165].

Different mechanisms participate in making the isoforms. The γ and β isoforms are made through multiple splicing of intron 9, ending with a different RD. In addition, by using an internal promoter, which is placed in intron four, isoforms such as Δ160 and Δ133 are made, which leak the TAD and a piece of the DBD. Furthermore, alternative initiation of translation at codon 40 or 160, bear the Δ40p53 & Δ160p53 [80]. Because of the isoforms origin of p53 proteins, some studies publicized that *TP53* mutations that ground mutated isoforms, which make mild to severe different cancer phenotypes, are a consequence of a solitary mutation in *TP53*.

3.6 Interaction

TP53 is responsible for encoding DNA-binding proteins to control gene expression activity to prevent mutations in the entire genome. Its product, the p53, stimuli or represses the expression of a diversity of important genes involved in apoptosis, cell cycle arrest, senescence, DNA repair and autophagy in reply to oncogenic or other cellular stress signals. It has been revealed that p53 interacts with several genes. Most of the p53-regulated genes in humans and mice are summarized in Table 2.

Table 2 shows p53 interactions with other genes.

Interactor Abbreviation [Reference]						
AIMP2 [166]	ANKRD2 [167]	APTX [168]	ATM [169-173]	ATR [169, 170]	ATF3 [174, 175]	AURKA [176]
BAK1 [177]	BARD1 [178]	BLM [179-181]	BRCA1 [178, 182-185]	BRCA2 [178, 186]	BRCC3 [178]	BRE [178]
CEBPZ [187]	CDC14A [188]	CDC14B [188]	Cdk1 [189, 190]	CFLAR [191]	CHEK1 [179, 192, 193]	CCNG1 [194]

CREBBP [195-197]	CREB1 [197]	circRNA_014511 [198]	Cyclin H [199]	CDK7 [199, 200]		
DNA-PKcs [170, 192, 201]						
E4F1 [202, 203]	EFEMP2 [204]	EIF2AK2 [205]	ELL [206]	EP300 [196, 207-209]	ERCC6 [210, 211]	
GNL3 [212]	GPS2 [213]	GSK3B [214]				
HSP90AA1 [215-217]	HIF1A [218-221]	HIPK1 [222]	HIPK2 [223, 224]	HMGB1 [225, 226]	HSPA9 [227]	HTT [228]
ING1 [229, 230]	ING4 [231, 232]	ING5 [231]	IκBα [233]			
KPNB1 [215]						
LMO3 [115]						
Mdm2 [195, 234-236]	MDM4 [237, 238]	MED1 [239, 240]	MAPK9 [241, 242]	MNAT1 [200]		
NDN [243]	NCL [244]	NUMB [245]	NF-κB [246]			
P16 [202, 236, 247]	PARC [248]	PARP1 [168, 249]	PIAS1 [204, 250]	PIN1 [251, 252]	PLAGL1 [253]	PLK3 [254, 255]
PRKRA [256]	PHB [257]	PML [235, 258, 259]	PSME3 [260]	PTEN [234]	PTK2 [261]	PTGG1 [262]
RAD51 [178, 263, 264]	RCHY1 [265, 266]	RELA [246]	Reprimo [267]	RPA1 [268, 269]	RPL11 [247]	
S100B [270]	SIRT1 [271]	SUMO1 [272, 273]	SMARCA4 [274]	SMARCB1 [274]	SMN1 [275]	STAT3 [246]
TBP [276, 277]	TFAP2A [278]	TFDP1 [279]	TIGAR [280]	TOP1 [281, 282]	TOP2A [283]	TP53BP1 [179, 284-289]
TP53BP2 [287, 290]	TOP2B [283]	TP53INP1 [291, 292]	TSG101 [293]			
UBE2A [294]	UBE2I [204, 273, 295, 296]	UBC [166, 260, 272, 297-301]	USP7 [302]			
WRN [181, 303]	WWOX [304]					
XPB [210]						
YBX1 [167, 305]	YPEL3 [306]	YWHAZ [307]				
Zif268 [308]	ZNF148 [309]					

Today, researchers have access to request the information related to their gene/s of interest with p53 from www.niehs.nih.gov/research/resources/databases/p53/index.cfm and www.targetgenereg.org free of charge. Notably, so long as p53 regulates a substantial array of genes by gene-proximal areas, it attaches to various more distant sites whose functions are more problematic to discern and may even regulate additional genes.

3.7 Post-Translational Modification

N-terminal and RD domains are subjected to a wide range of modifications. Multisite post-translation modification resembles a molecular switchboard that regulates p53 functions in responding to several signaling pathways, therefore, coordinates different signals for the precise control of p53 functions. The multi-modular form of p53 makes it an excellent site for many covalent modifications. So, it can be phosphorylated [310], acetylated [311], sumoylated [312], neddylated [313] and ubiquitinated [314]. Different modifications might be independent of each other and have different consequences. There is also an interplay between these modifications such that one modification event may promote or inhibit the other, or they may have additive effects, thereby quantitatively regulating protein functions [315].

3.7.1 Phosphorylation

Phosphorylation plays a major role in stabilizing p53 after DNA damage. Serine and threonine phosphorylation sites exist alongside the entire protein. But, they are enriched in the transcriptional activation region of TAD 1, TAD 2 and RD. Casein kinase I and II, DNA-protein kinase, and JNK1 can phosphorylate p53 at several sites. The MDM2 ubiquitin ligase can ubiquitylate the non-phosphorylated p53. The MDM2 disables p53 by 2 different mechanisms. First, it binds to N-terminal, preventing communication with the transcriptional machinery. Second, this attachment arbitrates the covalent attachment of ubiquitin to p53. Then proteasome degrades ubiquitylated p53. Hence, MDM2 acts as a *TP53* controller by targeting its destruction. In situations where cells face cytokines, hypoxia, metabolic changes, oncogenes, viral contagion, or DNA damage, although p53 ubiquitylation is suppressed and p53 increases in the cell's nucleus, where p53 is activated and stabilized through acetylation and phosphorylation and no longer responsible as a transcriptional activator when bound to MDM2. Furthermore, the protein regulates MDM2 activity in a negative feedback form. Thus, p53 activation ultimately leads to its inactivation by turning on a path that leads to its degradation. MDM2 is subject to further regulation by directly binding the active response factor protein, which stops MDM2-mediated p53 proteolysis. On the other hand, PTEN prevents MDM2-mediated degradation of p53. The p53 can transcriptionally activate phosphatase and tensin homolog, which may further inhibit protein kinase B function. Therefore, inhibition of protein kinase B function by inhibitors may provide positive feedback with possibly additional anticancer properties.

The c-Fos, a proto-oncogene, is also activated by the p53. Its phosphorylation takes place at the Serine 6, Serine 9, Serine 15, Serine 20, Serine 33, Serine 37, Serine 46, Threonine 18, Threonine 55, and Threonine 81 residues in N-terminal with some phosphorylation take places in the C-terminal linker and basic regions at Serine 315, Serine 371, Serine 376, Serine 378, and Serine 392. Phosphorylation at most of these sites is induced by DNA damage, and some such as Threonine 55 and Serine 376 are suppressed by genotoxic insult. At least ten cellular kinases such as Casein

Kinase-1-Delta, p38, and Jun NH2-terminal kinase are mediated phosphorylation. Notably, phosphorylation at Serine 15 by the ATM, ATR, either directly or by cell cycle Chk1/Chk2, or at Serine 20 by Chk1/Chk2 has been shown to alleviate the inhibition or degradation of p53, resulting in its stabilization and activation. The phosphorylation-induced p53 stabilization and activation are mediated through complex mechanisms and may differ based on the microenvironment or cellular setting. Hypoxia-inducible factor-1 (HIF-1) Alpha has been implicated to be intricate in p53 stabilization, but the mode of action is unclear. Recently, the interaction among them was reported to evoke HIF-1Alpha degradation. The Protein Inhibitor of Activated STAT (PIAS) protein family members have also been established to interact with p53. The PIAS1 and PIAS-Gamma role as SUMO-1 ligases for the p53 protein [316].

3.7.2 Acetylation

The primary non-histone protein is stated to be acetylated p53. Acetylation is an important modification of p53 and is independent of phosphorylation. The acetylation occurs in the DBD, RD and between these two domains. It is exactly acetylated at Lysine 320 by p300/CBP-associated factor and Lysine 370, Lysine 372, Lysine 373, Lysine 381, and Lysine 382 by p300/CBP. This process has been exposed to augment p53 DNA-binding and to arouse p53-mediated transactivation of its downstream target genes by recruiting co-activators. *In vivo*, oxidative stress, hypoxia, UV, and ionizing radiation induce acetylation at Lysine 320, Lysine 373, and Lysine 382. Acetylation upsurges p53 stability likely by inhibiting MDM2 binding to p53. Phosphorylation at N-terminal has been publicized to upsurge its communication with acetylase p300/CBP and to potentiate p53 acetylation. Acetylation also happened in K101, K120, K139, and K164 (in DBD). K101 acetylation is accountable for the regulation of p53 metabolic targets. So, mutations in K101 cause the failure of p53-mediated ferroptosis. K120 acetylation is critical for the selective induction of apoptosis and up-regulates the expression of PUMA, but it is unnecessary for p21 induction. Acetylation at K164 is vital for the induction of p53-mediated cell cycle arrest. It has been shown that mutations in K120 and K164 along with six RD lysine residues suppress the p53-dependent induction of p21. Notably, the six RD lysine residues mutant holds its DNA-binding ability and might persuade a p53-MDM2 feedback loop. The six RD lysine residues mutants are incapable of promoting apoptotic and cell cycle regulators, signifying that K120 and K164 are necessary for the action of its tumor suppressor ability. To date, the contribution of K139 to the selectivity of p53 target genes is unclear. Acetylation of lysine K320, K357, K319, and K305 residues have been found between RD and DBD. After DNA damage, K320 acetylation was found to suppress p53 pro-apoptotic activities. Acetylation at K357, K319, and K305 might also happen. But, the characteristics of K305, K319, and K357 residues are unclear and the enzymes catalyzing the acetylation of the last two residues have not been identified yet.

Deacetylation can be occurred by sirtuin1 and histone deacetylase-1 enzymes. The first one deacetylates p53 and has been proposed to moderate p53-dependent activities (e.g., DNA damage-induced programmed cell death). Deacetylation of p53 has been recommended to down-regulate the activation of *p21WAF1* and *Bax*. Activated p53 induces the transcription of many genes. After p53 is triggered it could be intricate in apoptosis, cell-cycle arrest, DNA repair, and stop blood-vessel creation [317].

3.7.3 Sumoylation

Sumoylation signifies enzymatic activities mediated by small ubiquitin-related modifier (SUMO) activating enzyme, SUMO-conjugating enzyme Ubc9, and SUMO E3 ligases that include 5 protein inhibitors of activated STATs (PIAS1, PIAS3, PIASy, PIASxα, and PIASxβ), and culminates in the creation of an isopeptide bond between the RD terminal glycine of a SUMO and the lysine residue of a protein substrate [318]. PIAS1 binds to the RD terminal of p53 [250, 319] and catalyzes the sumoylation [250], an alteration that represses the p53 function on a reporter plasmid having consensus p53 DNA binding sites [316]. However, investigations using the p21 promoter have publicized p53 transcriptional function upon communication with PIAS-1, even though this is independent of the RING finger domain and thus of p53 sumoylation. Remarkably, several proteins in the PML nuclear bodies are also sumoylation targets, similar to p53 [320].

3.7.4 Neddylation

Like other post-translational modifications, neddylation alters the conformation of target proteins, thereby affecting enzymatic function, communication with binding partners, and/or subcellular localization. Moreover, to its well-known responsibility in the action of Cullin-RING E3 ligases (CRLs) complexes, NEDD8 regulates many transcription factors by modulating intracellular transport and/or transcriptional action. Comparing the effects of conjugation of NEDD8 to non-choline targets, the most common consequence of neddylation is a change in protein stability, with neddylation targets typically stabilized by Ubl conjugation. For example, the neddylation of p53 prevents nuclear translocation and stops the transcriptional action of p53 [321, 322].

3.7.5 Methylation

The function of p53 methylation has not been clear either *in vitro* or *in vivo*. It is unknown whether it is related to the fine regulation of gene expression. Although it’s methylated in normal cells, its status in human cancers is unknown. Most p53 point mutations are placed in CpG sites with a mutation range consistent with 5-methylcytosine deamination. These hotspot codons encode arginine residues critical for p53 assembly and/or cellular responsibilities. Arginine could also be encoded by AGA and AGG, which have similar usage levels . in humans but are not aimed for methylation. The existence of a precise selection to preserve CGN is a controversial question. *TP53* mutations have always been identified at the protein level. Alteration of the methylation of a single CpG dinucleotide caused by a hotspot mutation is unlikely to have a cancer-specific result. However, biology is full of astonishments at all times and epigenetic rule/function is still in its infancy.

Methylation to arginine, histidine, and lysine is important for gene expression, regulation of protein activity, and RNA metabolism [323, 324]. Methyltransferases catalyze the protein's methylation by using S-adenosyl-L-methionine as a methyl donor [325]. Methylation produces the methylated substrate and S-adenosyl-L-homocysteine, which is then, degraded into adenosine and homocysteine by S-adenosyl-homocysteine hydrolase. In combination with other post-translation modifications, methylation of histones establishes the 'histone code' that determines chromatin structure and DNA availability for repair, replication, and transcription [326]. Histones are mostly methylated on arginine and lysine residues through histone arginine, and histone lysine methyltransferases. The last enzyme group transfer up to 3 methyl chains to the ε-nitrogen of lysine

residues making mono-, di-, or tri-methylated lysine. Except one, all the others contain a Su(var)3-9, Enhancer-of-zeste and Trithorax domain which is necessary for the binding of S-adenosyl-L-homocysteine and the interaction with the targeted lysine to catalyze the methyl transferase [327]. The histone lysine methyltransferases catalyze the methylation of p53 [328]. Arginine methyltransferases mediate the transferring of 1 or 2 methyl chains to the ω-nitrogen of the guanidinium lateral chain of arginine. Adding the second methyl chain to monomethylated arginine results in type I or type II protein arginine methyltransferases. Both types can catalyze the formation 5 of monomethyl arginine. To date, most of the eleven members of the enzymes are type I, including protein arginine methyltransferase1. Type II protein arginine methyltransferases are protein arginine methyltransferase 5, 7, and 9. The methyltransferase activity of protein arginine methyltransferase2, 10, and 11 has yet to be determined. It was thought that methylation was an irreversible modification for many years, until the identification of the Lysine-specific histone demethylase 1A [329]. It is a nuclear amine oxidase that uses flavin adenine dinucleotide as a cofactor to demethylate mono- and dimethylated lysines [329]. It demethylates histone H3 at K4 to induce transcriptional repression [330]. In addition, Lysine-specific histone demethylase 1A promotes androgen-receptor-dependent gene activation by demethylating histone H3 at K9 [331]. Interestingly, the Jumonji domain-containing family, has histone lysine demethylase activity, with different specificities for lysine sites and degree of methylation [332]. Identifying lysine-specific deamylase 1 and other lysine de-amylases generated great attention to finding the first arginine deamylase. Protein arginine deaminase 4 is the enzyme that converts arginine residues to citrulline. However, whether the enzyme also mediates the removal of methylated arginine *in vivo* is still controversial [333, 334].

3.7.6 Ubiquitination

Ubiquitination is the addition of ubiquitin, which comprises 76 amino acids, to a substrate protein. Proteins ubiquitination, mono and poly, contributes to various cellular procedures [335]. Ubiquitination is an extremely organized dynamic process [336]. The p53 and many items in the ubiquitination path are controlled by ubiquitin and ubiquitin-like proteins. Protein ubiquitination is in charge of a well-organized, structured, and reversible mode of action for regulating many cellular processes like cell signaling and trafficking, DNA repair, programmed cell death, and protein degradation [337-339]. The process is an enzymatically organized and regular event that implicates E1 activating enzymes, E2 conjugating enzymes, and E3 ubiquitin ligases [335]. The enzymes perform together in a cascade display to attach ubiquitin to a lysine residue on a target substrate. Ubiquitin is linked directly to lysine residues of the target substrate, known as monoubiquitination, or to another ubiquitin protein, known as polyubiquitination, by a covalent isopeptide bond. Monoubiquitination acts as a signaling event, to regulate several proteins, while polyubiquitination acts as a signal for degradation by the 26S proteasome. Lateral ubiquitination act as a regulator mode for p53 regulation. Polyubiquitination of p53 causes its degradation, but monoubiquitination regulates its nuclear export [340]. p53 mono and polyubiquitination are dynamic and reversible processes that have different roles in p53 activities. The first suggestion that the ubiquitination path regulated p53 was the documentation of the human papillomavirus E6-associated cellular protein [341]. It seizes E6AP to decrease p53 amounts as a replication mechanism in the host cells. Soon after, MDM2 was identified that ubiquitinates and degrade p53 without exogenous factors [342-

344]. Several studies have shown that MDM2 is the dominant and critical E3 ubiquitin ligase for p53 and that a very interesting novel gene domain mediates p53 ubiquitination. P53 and MDM2 act in a negative feedback loop, with p53 driving the transcription of *MDM2* during normal homeostasis and preserving low p53 amounts. However, upon any type of cellular stress and/or DNA damage, p53 amounts rise due to both the post-translational stopping of MDM2 function and disruption of p53-mediated *MDM2* transcription. The direct consequence of these cellular interactions was emphasized with the generation of *MDM2* null mice, which exhibit embryonic lethality at day E6.5. Homozygous tsg101−/−embryos failed to develop past day 6.5 of embryogenesis (E6.5), despite being reduced in size, and did not form mesoderm. Mutant embryos showed reduced cell proliferation *in vivo* and *in vitro*, but lacked increased apoptosis. Although p53 transcripts were not affected in tsg101-/-embryos, p53 was significantly stacked, suggesting altered post-transcriptional control of p53. Remarkably, lethality was completely reduced in a double knockout of *MDM2* and *TP53* mice [345-348]. Several mechanisms inhibit the p53-MDM2 interaction under cellular stress, signifying that the interaction is significant for regulating p53 homeostasis at any time in the cell. p53 phosphorylation at Serine 15 and Serine 20 in reply to DNA damage and even other sorts of cellular stress by ATM, ATR, Chk1, and Chk2, and DNA-PK is believed to abrogate the MDM2-p53 interaction, so stabilizing p53 [349]. Also, the p53 acetylation process which is significant for transcriptional action, takes place on the same RD lysine residues as ubiquitination [350]. Thus, this enzymatic procedure can compete with and block ubiquitination to induce p53 stabilization. In addition, there is also an indirect mode of action related to p53 stabilization. p53 can be stabilized by the tumor suppressor p14ARF in a binding way to it and stopping the physical interaction between the MDM2 and p53 [347, 348]. Although p14ARF is a nucleolar protein, MDM2 sequestration and subsequent p53 stimulation occur inside and outside the nucleus [351, 352]. In addition, p14ARF could stop and inhibit MDM2 in response to improper oncogenes, which provides the cell with a response mechanism activating p53 to this type of cellular stress [348].

The MDM2 ubiquitinates p53 takes place at lysine K370, lysine K372, lysine K373, lysine K381, lysine K382, and lysine K386 in the RD [353, 354]. Knock-in investigations confirmed that wherever lysine was replaced with arginine (p53-6KR mutant) *in vivo*, p53 expression levels did not change dramatically, suggesting that despite lysine being required for p53 regulation and function but not sufficient for degradation [355, 356]. The *in vivo* half-life of the p53-7KR mutant, which is the murine equivalent of the p53-6KR mammalian mutant, was also revealed to be comparable to the WT p53 [356] signifying that alternative sites on p53 might be substantial for its stabilization. In addition, it was revealed that p53 could also be ubiquitinated *in vitro* within the DBD [357]. Once DBD was removed, the total ubiquitination and p53 stabilization decreased. Nevertheless these sites were also not enough for the entire p53 degradation. Ubiquitin-like proteins can be targeted p53. SUMO and NEDD8, both evolutionarily conserved in eukaryotes, are similar to ubiquitin in their three-dimensional structure and mode of action by lysine [358-360].

Deubiquitination enzymes are specifically able to eliminate ubiquitin moieties from p53. HAUSP (herpesvirus-associated ubiquitin-specific protease) stabilizes p53 even in the presence of excess MDM2 and also induces p53-dependent apoptosis. Also, it has an intrinsic enzymatic ability that exactly deubiquitinates p53 both *in vitro* and *in vivo*. In contrast, expression of a catalytically inactive point mutant of it in cells upsurges the amounts of p53 ubiquitination and destabilizes p53. These results suggest how p53 could be stabilized by deubiquitination directly [302]. The HAUSP could cleave ubiquitin off p53, thus saving it from proteasome-dependent degradation. This is how p53 is

stabilized in response to oncogenic insults [361]. HAUSP is mostly localized in the nucleus, so a fraction exists in cytoplasm and mitochondria. Overexpression of it causes p53 stabilization but depletion does not end with a reduction in p53 amounts but rather raises p53 levels due to its attachment with MDM2 and MDM2 deubiquitination. In unstressed cells it has been stated that HAUSP is a better binding associate with MDM2 than p53. Also, in unstressed cells ubiquitin Specific Peptidase 10 is located in the cytoplasm and deubiquitinates cytoplasmic p53, reversing MDM2 ubiquitination. After DNA damage, Ubiquitin Specific Peptidase 10 translocates to the nucleus and participates in p53 stabilization but does not interact with MDM2 [362].

3.8 Aggregation

p53 aggregates are heterogeneous assemblies of amorphous aggregates, amyloid-like fibrils and oligomers which can change p53 oncogenic function. In cancers, p53 aggregates causing functional gene changes and cancer progression. The existence of these assemblies in cancer tissues, the *in vitro* capability for p53 mutants to co-aggregate with the WT, and the detection of cell-to-cell transmission testify that cancer has the basic characteristics of prion and prion-like illnesses. p53 aggregation has been found in breast and colon cancers, and WT p53 was found to be aggregated in neuroblastoma, and retinoblastoma. Cancers with *TP53* mutations might share a common propagation mechanism with prion-like illnesses. In these illnesses, insoluble protein aggregates accumulate inside or outside the cells. Prion-like characteristics for p53, based on the fact that it can spontaneously aggregate, these aggregates can penetrate cells and co-aggregate with cellular p53. It has been revealed that recombinant exogenous WT p53 aggregates generated *in vitro* can penetrate cells by macro-pinocytosis and induce aggregation of endogenous WT p53. This result reveals a key feature of p53 aggregates and supports their prion-like character. So, the inhibition of the WT p53 aggregation appears to introduce a hopeful strategy for therapeutic intervention in patients facing cancer. In brief, the cancer suppressor p53 characteristics include its prion-like properties and cellular uptake mechanisms, which are related to its GOF and associated with cancer formation and malignancy. Thus, small molecules that bind to p53 and prevent its aggregation may represent a suitable strategy to prevent cancer.

Aggregation of mutant p53 in the associated oncogenic GOF, i.e., the acquisition of actions that promote cancer growth, chemoresistance and metastasis. For example, co-sequestration of mutant and WT p53 into inactive cellular inclusions might end with overexpression of antiapoptotic and pro-proliferative genes earlier repressed by p53. Aggregation of mutant p53 also makes misfolding of p63 and p73, which are then incorporated into the inclusions, facilitated through interactions of the aggregation-prone core of p53 DBD with near identical segments existing in the p63 and p73 DBDs. p63 and p73, which are not often mutated in cancers, have partial functional overlap with p53. However, co-aggregation with mutant p53 suppresses the regulatory functions of p63 and p73, ending with deficient transcription of target genes involved in apoptosis and cell growth control, which leads to uncontrolled proliferation, invasion, and metastasis. Moreover, aggregation of mutant p53 has been known to induce overexpression of Hsp70, which promotes apoptosis and cancer cell proliferation. Hence, the amyloid-like aggregation of mutant p53 might contribute to its oncogenic GOF and cancer suppressor function. Of relevance, it takes the place of hydrophobic amino acids in the aggregation-prone core of p53 DBD with arginine residue repeals co-aggregation of mutant form with WT protein and its family members, p63 and p73, along with eliminating

overexpression of Hsp70. Notably, a p53 DBD-derived peptide harboring the aggregation-suppressing I254R mutation was shown to prevent mutant p53 aggregation, abrogate oncogenic GOF, and inhibit binding of mutant p53 with p63/p73 by masking the aggregation-prone core, which restored the mutant protein to a WT p53-like functionality and reduced cancer cell proliferation *in vitro* and halted cancer progression *in vivo*. So, it indicates that targeting mutant p53 aggregation is an effective and viable chemotherapeutic approach. Like WT p53 its mutant exhibits the singular property of spontaneously losing DNA binding activity at 37°C.

3.9 Roles in Cells

3.9.1 Metabolism

The importance of the activities of this protein in cell metabolism has been determined [363]. Under normal physiological conditions, specific p53 functions participate in the homeostatic regulation of metabolic processes, and these functions are important for cancer prevention [364]. In cells p53 regulates glycolysis, lipid metabolism, nucleotide synthesis, oxidative phosphorylation, and pentose phosphate pathway [365]. WT p53 restricts lipid synthesis and glucose metabolism, but its mutated form has been shown to do the opposite [366]. Current investigations have stated that GOF mutant p53 proteins drive metabolic reprogramming in cancerous cells that promote cancer progression. About energy metabolism, p53 has been publicized to reduce glycolysis and promote mitochondrial respiration [367]. It also involves amino acid, fatty acid, and nucleic acid metabolism, antioxidant capacity, mitochondrial quality control, and autophagy [368]. Its association with ceramide metabolism to DNA damage response by alkaline ceramidase 2 has been revealed [369]. Its role in metabolism and diabetes has been reviewed recently [370]. It regulates antioxidant defense, glycolysis, glutamine metabolism, and mitochondrial oxidative phosphorylation. By regulating these metabolic processes, p53 maintains redox balance and cellular metabolism homeostasis in the cell, significantly contributing to its role as an oncogene [371, 372].

3.9.2 Aging

Its regulation of aging via its transcriptional adjustment of cellular metabolism has been reviewed [373, 374]. Another review was done by Lopez-Otin *et al.* which explained the connection between WT p53 and aging [375]. The authors agreed on 9 key signs of aging. Notably, the p53 path was a key organizer of at least 3 signs including cellular senescence, genomic instability, and mitochondrial dysfunction. p53 also has a central function in regulating paths that contribute to the immune system and metabolic signaling, which may help to understand the mechanisms contributing to the aging process.

3.9.3 Reproduction

p53 adjust maternal reproduction [376, 377]. Its novel role in regulating maternal reproduction in mice has been documented by leukemia inhibitory factor (LIF), a novel p53 target gene [378]. Sufficient amounts of uterine LIF should be required for the blastocysts' implantation or early embryos into the uterus. It has been stated that p53 deficient [p53(-/-)] female mice have an abridged chance of pregnancy rate and litter size, due to impaired implantation as a consequence of decreased uterine LIF amounts. LIF brings back maternal reproduction chance by improving

implantation after administration to pregnant [p53(-/-)] mice. An association among women carrying p53 codon 72 polymorphism with recurrent implantation disappointment has been reported, suggesting that LIF plays a similar role in humans [378]. Some studies have documented that the proline allele is enriched in patients undergoing IVF [379, 380]. Studies on p63- and p73-knockout mice have shown the participation of both proteins in the female reproduction system and their function in egg formation and apoptosis related to p63, and spindle checkpoint related to p73 in female mice. Selected alleles of SNPs in both related genes were enriched in IVF patients. These findings suggest that p53 family members participate in multiple stages to regulate the female reproductive system in humans [381]. The roles of the p53 proteins family and the potential effect of p53 polymorphisms on reproduction have been reviewed [382].

3.9.4 Hypoxia

Subjecting oncogene-transformed cells to hypoxic stress induces p53 accumulation and activates the p53-dependent apoptosis paths. However, this stress does not induce p53-dependent cell cycle arrest, signifying that p53 function is differentially regulated by DNA damage and hypoxic stress. Hypoxic stress has been revealed to induce p53 accumulation, but unlike DNA damage, it cannot induce endogenous p53 effector mRNAs and proteins. It does not prevent the triggering of p53 target genes by ionizing radiation, signifying that p53-dependent transactivation requires a DNA damage-inducing signal that is absent under the lack of oxygen condition itself. DNA damage also causes the interaction of p53 with the transcriptional repressor mSin3A and the transcriptional activator p300. But hypoxic stress mainly causes the interaction of p53 only with the first one. Studies have shown that pre-treatment of cells with a histone deacetylase inhibitor, which relieves transcriptional repression, significantly reduced p53-dependent trans-repression and hypoxia-influenced apoptosis. Genotoxic stress triggers both interactions, whereas stresses that lack a DNA damage component, as characterized by hypoxia, primarily induce interactions with inhibitors. However, inhibition of either type of interaction can lead to reduced apoptotic activity.

The p53 protein acts as an emergency brake on cancer development by killing cells that try to proliferate in areas of oxygen deficiency. But cells with p53 mutation can survive in these conditions [383]. Inhibitors of angiogenesis suppress tumor growth by inducing hypoxia [384]. Severe hypoxia induces moderate stabilization of WT p53, partly due to the induction of HIF-1. In addition, it can downregulate MDM2, thus causing p53 cumulation [385, 386]. Like p53 and MDM2, HIF-1 is degraded by the proteasome [385]. Furthermore, MDM2 could target HIF-1 for degradation [387]. Given that MDM2 is up-regulated by p53 and that MDM2 targets for degradation both HIF-1 and p53, one event can foretell the following phenomena is either i) HIF-1 causes WT p53 stabilization because of sequestration of MDM2 or ii) WT p53 causes HIF-1 destabilization because it triggers MDM2 [388].

3.9.5 Autophagy

Autophagy is a dynamic cellular procedure in which cytoplasmic contents consisting of damaged organelles, and old proteins are enclosed in bipolar vesicles and after joining the lysosome, are broken down and generate energy [389-391]. This process absorbs, breaks down and recycles actin, actin filaments, centromere, centrosome, chromosome, cytoplasm, cytoskeleton, cytosol, endoplasmic reticulum, endosome, eukaryote, Golgi apparatus, intermediate filaments,

intermembrane space, microtubule, matrix cytoplasm, nucleus, organelle, peroxisome, ribosome, rough and smooth endoplasmic reticulum to keep metabolic homeostasis and regulate protein and organelle quality [392]. The process is frequently used to maintain cellular survival [390]. However, the progress of autophagy can lead to cell death. The autophagy process should be separated into 4 stages including i) induction of autophagy, ii) the formation of autophagosomes, iii) decomposition of contents within autophagosomes, and finally iv) release of macromolecules from auto phagolysosomes. There are also various cellular pathways involved in the induction of autophagy, including the p53/p73 family pathway, Raf/MEK/ERK, PI3KI/Akt/mTOR, PI3K III/BECN1, and death-associated protein kinase pathway [393, 394]. It is noteworthy that autophagy always occurs at a basic level in normal tissues to maintain homeostasis and normal cell function, but it plays a dual role in stressful situations. Autophagy could lead to increased cell survival or a program of cell death, but no specific mode of action has been proposed to differentiate between the two kinds of it. Autophagy suppresses p53 and also p53 activates autophagy. Suppression of p53 by autophagy is significant for cancer promotion and for preventing tissue degeneration. On the other hand, activation of autophagy by p53 suggests that autophagy is part of the protective function of the p53 protein. One of the p53 target genes is a damage-regulated autophagy modulator. The induction of this gene expression promotes the process of autophagy [395]. Induction of apoptosis by p53 appears to be mandatory in the cells, although the mechanism is unclear [395]. Interferon Stimulated Exonuclease Gene 20kDa-Like 1, a p53 target gene, enhances autophagy [396]. Overexpression of the gene enhanced apoptosis and autophagy, partially rescued by Atg5 deficiency. Unc-51, like autophagy-activating kinase 1 and autophagy-related 7, is among the genes directly activated by p53 [397]. p53 induction in this situation persuades autophagy. The functional significance of p53-induced autophagy revealed the induction of apoptosis in reply to DNA damage and repression of transformation by adenovirus early region 1A and H-ras [397]. Addressing p53 transcription-mediated autophagy in physiological settings *in vivo* is critical. By improving transgenic mouse models for provisional and systemic inactivation of autophagy *in vivo*, autophagy-deficient and autophagy-deficient WT mice show different responses to DNA damage that differ from the absence of p53 [398]. In contrast to direct transcriptional initiation of autophagy by p53, p53 deficiency induces pro-survival autophagy [399]. Lack of p53 might induce stress that requires repair through autophagy. These two can be elucidated by deleting a critical autophagy gene in mice with or without combined deletion of p53 to address the functional outcome. Non-transcriptional mechanisms by which p53 can adjust autophagy have also been described [399, 400], and it will be interesting to determine the physiological context in which these actions might be significant. Autophagy suppresses p53 in cells, and regardless of the mechanism, its inhibitors likely exert anticancer effects in part by acting as p53 activators [392].

3.9.6 Stemness

Stem cell liability, collectively known as stemness and senescence, appears to be adjusted by overlapping signaling networks. Aging-related signalings such as p53, p21Cip1 or Bmi-1, p16Ink4a have critical functions in stem cell maintenance by preventing premature exhaustion. In cancer cells, increased stemness may have profound consequences for cancer invasion and clinical outcomes [401]. Despite abundant evidence linking the loss of p53 to stemness-like phenotypes in cancer cells, it remains unclear how p53 contributes to stemness acquisition at the molecular level. However,

since reprogramming demonstrates the acquisition of a less differentiated state by differentiated cells, the results suggest that p53 might influence the balance between stemness and differentiation by regulating G1 progression. Aging is associated at once with the stem and with the potential to develop highly aggressive types of cancer [401]. WT p53 prevented the reprogramming of mouse embryonic fibroblasts toward induced pluripotent stem cells [402-406]. Mutant p53 promotes somatic cell reprogramming compared to knock-out cells [407].

3.9.7 Chemoresistance/Radioresistance

A rising number of investigations proposed that the nature of a p53 mutation could influence cellular functions, clinical responses to chemo/radiotherapy and, the prognosis of cancer [408-410]. As a result, p53 has an essential responsibility in chemotherapy for cancer clinical management [411]. The protein facilitates desirable anticancer drug response by various types of critical cellular activities corresponding to apoptosis [411]. Alterations of these activities lead to greater chemoresistance [412, 413]. Four different mechanisms of mutant p53 have been recognized [414]. In addition, another well-known mechanism for mutant p53 related to chemoresistance is the activation of the *MDR1* gene [415].

Mutations in p53 might happen due to an irregularity in the position of any amino acid [416]. Chemoresistance is also seen in cancerous cells harboring WTp53 so it can be important, particularly when cancerous resistant cells harbor WT53. This represents a paradox because it differs from the established performance of this genotype in easy response to anticancer drugs. Furthermore, cancerous-resistant cells expressing WT could be much greater than in cancerous cells expressing the mutant form, leading to the identification of the WT p53 GOF phenotype, and it is tempting to speculate that the chemoresistance interactions may be the result of GOF's association with WT p53. Furthermore, one explanation for why cancerous cells containing WT p53 show chemoresistance may be flawed involving other players of the p53 path. Two studies investigated whether defects in cell cycle checkpoint kinase 2 or ATM or, might replace TP53 mutations and render cancerous-resistant cells. Indeed, rare but nonsense mutations in the cell cycle checkpoint kinase 2 gene may replace *TP53* mutations that cause anthracycline resistance in patients with primary breast cancer [417, 418]. These mutations caused early stop codons with a whole loss of protein expression. In contrast, cancers that contain abnormal mutations in cell cycle checkpoint kinase 2, including I157T, show a high risk of developing breast cancer that appears to respond typically to chemotherapy [419]. Among anthracycline-resistant cancers lacking mutations in the cell cycle checkpoint kinase 2 or *TP53*, one study found low levels of ATM expression (but not *ATM* mutation) to guess anthracycline/mitomycin resistance [420]. These results link the *ATM* and the *cell cycle checkpoint kinase 2* to p53 activation in response to DNA damage in breast cancer. They may be of significant importance for understanding cancer biology and chemotherapy. Chemotherapeutic agents, for example 1R, 2R-diaminocyclohexane (trans-director) (dichloro) platinum (IV), are available. There is evidence that action against such cancers is likely. However, recognizing this increased chemoresistance phenotype is the first step towards elucidating the complex mechanisms and thus establishing rationale-based chemotherapeutic agents crucial for achieving ultimate success in the clinical setting against this phenotype. Some clinical trials have implicated some important p53 activators such as MI-77301, PRIMA-1Met, RO5045337, and RO5503781 . Recently, small molecules capable of silencing the function of MDM2 have been

identified. For example, a novel MDM2 antagonist, MI-77301 enhanced the activity of combination therapy with conventional chemotherapeutic agents. However, only a few agents have favorable pharmacokinetic properties and acceptable toxicity profiles, and further research is desirable.

It has been reported that *TP53* mutation is associated with increased radioresistance in rhabdomyosarcoma and Ewing's sarcoma. Innovative strategies to overcome this type of resistance are necessary to improve outcomes in p53-disrupting rhabdomyosarcoma and Ewing's sarcoma [421].

3.10 Restore Strategies

The cumulative amount of p53 should be possible for cancer prevention or treatment. However, this is not a clinical strategy, as it may initiate premature aging [422]. Restoring p53 normal activities brings some promise [423]. Researchers have revealed that this strategy could lead to the regression of cancerous cells without hurting normal cells. The ways in wherein cancer regression happens depend mostly on the cancer type. For instance, restoring endogenous p53 action in lymphomas induces apoptosis, while cell growth may be reduced to normal. Therefore, pharmacological reactivation of p53 offers an opportunity [424, 425]. Small molecules that directly target mutant p53 via reactivation of its tumor-suppressive transcriptional function are chetomin (for R175H mutant),COTI-2 (for R175H, Y220C, R248Q, I255N, and R273H mutants), CP-31398 (for V173A, S241F, R249S, and R273H mutants), KSS-9 (for R175H mutant), MIRA-1 for (R175H, R248Q, and R273H mutants), P53R3 (for R175H, R273H, R248W, M273I mutants), PEITC (for R175H mutant), PhiKan083 and PhiKan7088 (for Y220C mutant), PhiKan11007 (for Y220C and V143A mutants), PRIMA-1 (for R273H, R175H, and R248Q mutants), PRIMA-1Met (for R273H and R175H mutants), ReACP53 for (R175H and R248Q mutants), RETRA (for R273H, R248Q, R280L, and G266E mutants), RITA (for R175H, R248W, R273H, and R280K mutants), SCH529074 (for R175H, L194F, R248W, R249S, and R273H mutants), stictic acid (for R175H and G245S mutants), STIMA-1 (for R175H and R273H mutants), and zinc metallochaperone-1 (for R175H mutant).

The first commercial gene therapy agent was Gendicine®. In 2003 it was permitted for treating head and neck squamous cell carcinoma in China. It carries a functional copy of the *TP53* using an engineered adenovirus [426].

The p53 protein is continuously produced and degraded in healthy cells, and as a result its fluctuations are reduced. Degradation of it is related to MDM2 binding in a negative feedback form, MDM2 itself is induced by p53. Mutated p53 proteins are often unable to activate MDM2 and cause the accumulation of p53 in cancer cells. They are characteristically unstable in healthy cells, and they can accelerate tumor development once it is stabilized. Small molecules that directly target and degrade mutant p53 are gambogic acid (for R175H, G266E, R273H, and R280K mutants), HSP90 inhibitors (for R175H, L194F, R248Q, R273H, and R280K mutants), histone deacetylase inhibitors (for R175H, R280K, V274F, and P223L mutants), MCB-613 (for R175H mutant), spautin-1 (for R175H/C/D, S241F, R248Q/W/L, G245C, E258K, R273H/L, R280K, and R282W mutants), statins (for V157F, R172H, R175H, Y220C, R248W, R273H, and R280K mutants), and YK-3-237 (for V157F, M237I, R249S, R273H, and R280K mutants). Furthermore, the mutant form itself can inhibit p53 in normal amounts. Sometimes single missense mutations disrupt p53 stability and activity [78]. The dynamics of p53 proteins, together with its antagonist MDM2, show that the amounts of it, per unit concentration, fluctuate as a function of time. This "damped" oscillation has been both clinically

documented [427, 428] and mathematically modeled [427, 429]. Precise statistical models also showed that the concentration of p53 fluctuates much more quickly when cells face double-strand breaks or UV light. This supports and models the understanding of p53 regulation in reply to DNA damage, where p53 is activated. Chemicals that block MDM2-P53 interaction and reactivate TP53 are HLI98 compounds with 5-Deazaflavin chemical structure, MI-219 and MI-319 (MDM2-P53 interaction inhibitor) with Spiro-oxindole chemical structure and Nutlin-3 (MDM2 antagonist) with *cis*-imidazoline chemical structure. Chemicals that block MDM2-P53 interaction and reactivate TP53 are HLI98 compounds with 5-Deazaflavin chemical structure, MI-219 and MI-319 (MDM2-P53 interaction inhibitor) with Spiro-oxindole chemical structure and Nutlin-3 (MDM2 antagonist) with *cis*-imidazoline chemical structure.

In brief, today's pharmacological strategies for targeting WT p53 focused on small molecules. They target WT p53 activation via binding to p53 such as RITA, inhibition of MDM2/X such as dual inhibitor ALRN6924 and the MDM2 inhibitor outline-3, and TENOVINs. Small molecules target mutant p53 via restoration of p53 function are PRIMA-1, degradation of mutant p53 via activation of MDM2 such as 17AAG and NSC59984 or interruption of mutant p53-p73 interaction such as RETRA. Mutant p53 is more stable than WT p53 in human cancerous cells, due to the interaction of mutant form with the HDAC6/HSP90 chaperone complex. Treatment of cancer cells with 17-AAG promotes the degradation of various p53 mutants by inactivating HSP90 and decreases the viability of the cells carrying mutant form. Ganetespib, a unique triazolone-containing Hsp90 inhibitor, displayed >50-fold more potency than 17-AAG in degrading P53R175H and P53R248Q using mouse models.

Activation of p73 upregulates p53 target gene expression and induces cell death. Biotherapeutic approaches are based on gene transfection and genomic modifications. p53 is transfected into cancer cells with an adenovirus to replace mutant p53, and upregulates p53 signaling (such as rADp53). Genomic editing is used to restore wild-type p53 or delete mutant p53 in cancer cells by genome editing approaches (such as CRISPR). A bispecific antibody with mutant p53-specific peptide and ALH ligands promotes T cells to recognize and kill p53-mutant tumor cells in cancer immunotherapy. Anticancer agents with anti-aggregation properties are classified into 4 sets. 1) Agents with chaperone-based mechanisms; 2) Designed peptides; 3) Thiol alkylating agents; and 4) Miscellaneous compounds with anti-protein aggregation properties that have been studied in neurodegenerative diseases. Furthermore, autophagy as a possible degradation pathway for aggregated p53 was highlighted.

3.11 Chaperoning the WT p53

Heat shock proteins (HSPs) are encoded by genes whose expression is significantly increased during stress conditions, such as heat shock, alcohol, fever, inflammation, heavy metals, inhibitors of energy metabolism, and oxidative stress. Under these conditions, HSPs increase cell survival by keeping and disaggregating stress-labile proteins and the proteolysis of the damaged proteins. Under non-stress conditions, HSPs have multiple housekeeping activities, such as folding and translocating newly synthesized proteins, activation of specific regulatory proteins, including transcription factors, replication proteins and kinases, protein degradation, protein signaling, including steroid hormone activation and tumor immunogenicity, and antigen presentation. They act as chaperones to protect important proteins such as p53 from degradation, to control the quality

of protein folding, and to deliver misfolded or damaged proteins to the proteasome for disposal, thus vouchsafing cell viability under these conditions Tumor suppressor p53 (p53), the most frequently mutated gene in human cancers, is one of the proteins that functionally interact with HSP40/JDPs.

Organized networks of HSPs with molecular chaperone action guard cells from sudden conservational changes. In addition, molecular chaperones are essential during stress-free conditions, where they moderate housekeeping functions i.e., protein folding, degradation, and translocation. The HSP family is subdivided into HSP110 (HSPH), HSP90 (HSPC), HSP70 (HSPA), HSP40 (DNAJ), small HSPs (HSPB), and the chaperonin family proteins HSP60/HSP10 (HSPD/E) and TRiC (CCT). HSPs are classified by their molecular weights in kDa. Under stress conditions HSPs play several roles in proteostasis maintenance, such as prevention of protein aggregation and dissociation of existing aggregates, refolding of stress-damaged proteins, native protein conformation and activity maintenance, and inhibition of apoptosis. These chaperone networks are widely remodeled during tumorigenesis, so they are advantageous to the transforming cell. By buffering necessary signaling pathways, molecular chaperones empower cancer evolution, leading to the chemoresistance of cancer cells. Controversially, the same molecular chaperones, indispensable for p53 in reaching its tumor suppressor potential, are useful in adopting an oncogenic GOF phenotype when *TP53* is mutated. On the molecular level, HSPs by unwinding the mutant p53 protein expose aggregation-prone sites leading to the sequestration of other tumor suppressor proteins causing inhibition of apoptosis and chemoresistance. A remark that somewhat shows the nature of mutant p53 pro-oncogenic function modifiers, is the fact that transgenic *Hsf1*-knockout, Trp53 R172H mice do not develop cancer. HSF1 transcription factor extensively controls HSPs synthesis. This suggests that HSPs might contribute to mutant p53 stabilization and cancer progression. Mutated p53 R175H was found to form a stable complex with HSP40, HSP70, HOP and HSP90. Elevated levels of one or more major HSP classes (e.g., HSP90, HSP70, HSP60, HSP40, HSP27) have been documented in many types of cancers. In breast cancers, HSP70 overproduction correlates with metastasis and poor prognosis. Moreover, overexpression of HSP70 induces cellular transformation. In mouse models it has been shown that the γ-irradiation stabilizes mutant p53 and shifts the cancer phenotype to more aggressive, compared to knock-out mice treatment. It is tempting to speculate that similar phenomena might happen in human patients who harbor mutated p53 and are treated with γ-irradiation. Therefore, the knowledge of patient p53 status, and MDM2 protein levels may be crucial in devious the optimal therapeutic strategies. Based on the recent findings it has been suggested that HSP70 inhibitors could be used synergistically with γ-irradiation in the treatment of patients with mutated p53. Like other proteins, mutant and WT p53 could be misfolded under heat shock and genotoxic stress. These misfolded proteins like correctly folded native proteins are detected by molecular chaperone systems, including HSPs, to be degraded, refolded, and stabilized. Indeed, both mutant and WT p53 are bound to and functionally regulated by the HSP system. So, this system has an important impact on the protein levels and functions, understanding the mechanisms by which HSPs detect and regulate the structure and functions of WT and mutant p53 would help design efficient p53-targeted anti-cancer agents. No less than 50 members of HSP40/JDPs are present in cells, each with different clients. This may explain the diverse regulation of target proteins including p53 by HSP40/JDPs and different biological results. More than a few pieces of the literature suggest HSP70-independent functions of

HSP40/JDPs in *vitro* and *in vivo*. Hence, whether the oncogenic or tumor suppressive functions of each HSP40/JDP are HSP70-dependent or -independent needs to be explained shortly.

3.12 Personalized Medicine

Somatic mutations are transferable to the next generation. These mutations are important because the transformation of a normal cell into a cancerous form occurs sequentially through several separate genetic events. Whether a biomarker is prognostic or predictive is often unclear, although such information is critical to evaluating the clinical value of a cellular marker. Knowing the patient's genetic map may help clinicians choose the individual chemotherapy or treatment and prescribe it with the right regimen [430]. The benefits obtained in colon cancer survival have been extended to the breast, cervix, prostate, and skin. Considering the Vogelstein model's emphasis on the accumulation of cancer mutations, comprehensive genomic profiling may be performed to identify their unique cancer mutation landscape once screening methods identify cancers. If sequencing reveals the presence of targetable mutations, patients are selected to receive the most appropriate treatments, thus providing a personalized medicine approach.

There is no doubt that the future of successful cancer treatment will rely on medical information, individual and population genetics, and new drugs will be purposefully prepared and prescribed based on the individual's and tissue's genetic makeup for successful treatment and fewer side effects.

4. Future Perspectives of Studying p53 in Medicine

The wide variety of p53 regulatory mechanisms and their collaboration in triggering specific responses remain an open area for research. This area consists of expanding gene therapy approaches focused on p53 expression, p53 regulation, mutant inhibition of p53 GOF, and activation of WT p53 function by finding small molecules that reactivate it. Overcoming chemoresistance to traditional chemotherapeutic agents with the development of synergistic combinations with innovative targeted small molecules can potentially improve chemotherapy/radiotherapy activities and outcomes. Perhaps the use of combination therapies that target both mutant p53 proteins and pathways controlled by non-coding RNAs may be a new chemotherapeutic treatment strategy. In addition, p53 family members make many related but functionally diverse proteins, further complicating the responsibility of p53-related proteins in cancer progression, growth, autophagy, and aging. Finally, new technologies, personalized medicine, digital therapies, 3D printing, immunotherapy, nano-therapy, gene and stem cell therapies, artificial intelligence, and wearable and implantable sensors have arrived or are on the way. These opinions, views and approaches have further stimulated future research on the p53 gene/protein.

5. Conclusion

The *TP53* and its product p53 protein have been discovered and extensively studied by researchers. p53 gene/protein has been found to perform an undeniable role in the biology of cancer and aging. Although researchers' efforts have helped clarify the structure, function, and regulation as well as other aspects of the *TP53*, they have created more ambiguities and questions about the gene and its product. Identifying various p53 isoforms, the discovery of natural antisense,

WraP53, and the important roles of *TP53* in processes such as aging, longevity, and metabolism have made p53 an intelligent molecule. Cancer cells with defects in *TP53* and the introduction of small molecules that activate mutated p53 or inhibit *MDM2*, are among the cancer treatments developed based on p53 biology.

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