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Comprehensive Roles of *TP53* in Cell Signaling, Apoptosis and Carcinogenesis – A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author SA supervised the work. Author ZSB managed the literature searches and edited the manuscript. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

TP53 gene is a tumor suppressor gene and it inhibits the emergence of cancerous growth. The signaling of *TP53* takes part in the co-ordination of cellular response to various kinds of stress like hypoxia and DNA damage. The downstream signals start to multiple processes such as MTOR (mechanistic target of rapamycin), apoptosis, and the arrest of cell cycle. *TP53* becomes inactivated when encounters tumor growth. According to estimation, more than half of all cancers imply the inactivating mutations of *TP53*, which leads to the expression of mutant p53 protein. An extensive range of cancers carry the mutations of *TP53* or certain other defects which deregulate p53 and its cofactors, making this gene a significant and highly studied tumor suppressor gene. Most of the mutations that are found in human cancers are not inherited but are acquired. As p53 protein binds DNA, it triggers another gene to synthesize a protein named p21 inside the cell, which interferes with a cell division-stimulating kinase (cdk2). When p21 forms a complex with cdk2 the

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cell cannot pass onto the next phase of cell division. Therefore, Mutant p53 can no longer get itself attached to DNA effectively, and as a result, the p21 protein is not made available to function as the 'stop signal' for the division of cell.

Keywords: Suppressor gene; apoptosis; cell signaling; carcinogenesis; gene therapy; drug therapy; genome.

1. INTRODUCTION

The tumor suppressor gene *TP53* is also known as the “guardian of the genome,” because it maintains genetic stability and prevents the formation of tumors. After the cell injury, when p53 is activated, it induces numerous cellular responses, like cell repair and survival or even programmed death of the cell [1]. Changes in different cell-signaling pathways can lead to the deregulation of apoptosis and result in the cancer [2]. Tumor suppressor gene *TP53* is a component of transcription, which controls the cell cycle. *TP53* switches on the protein, which are involved in the repair process of DNA but if DNA has damaged for long, it halts the cycle of the cell at the G1/S phase, and initiates apoptosis if DNA damage becomes irreversible. Carcinogenesis takes place if this system goes out of control. *TP53* gene works resembling brake pedal of a car (Fig. 1). Normally, it retains the excessively fast multiplication of the cell, similar to how a brake stops car from moving speedily.

If someone receives justa single copy of functional *TP53* gene from biological parents, he is more susceptible to cancer and normally develops a number of independent tumors in different tissues at young age. Such situation is unusual, and recognized as (LFS) Li-Fraumeni syndrome. Nevertheless, abnormalities in *TP53* play a part in complicated series of molecular occurrences towards the emergence of tumor [1]. Furthermore, apoptosis is considered as a carefully controlled energy-dependent process, distinguished by particular biochemical and morphological features, which involves the activation of the caspase (enzyme) [3]. p53 is a crucial suppressor protein in apoptotic pathways. It is located at the crossroads of signaling mechanisms, which are important to keep the apoptosis and cell growth regulated initiated by genotoxic and non-genotoxic stresses. *TP53* is a tumor suppressor gene, whose expression corrects DNA mistakes, declines the cell division, or inform cells when to die (a process referred to as *programmed cell death* or *apoptosis)* [3]. When *TP53* genes do not function appropriately, growth of the cells become impossible to manage, which can lead to tumor formation. The malfunctioning of *TP53* results in enhanced tumor growth because of reduced apoptosis [3].

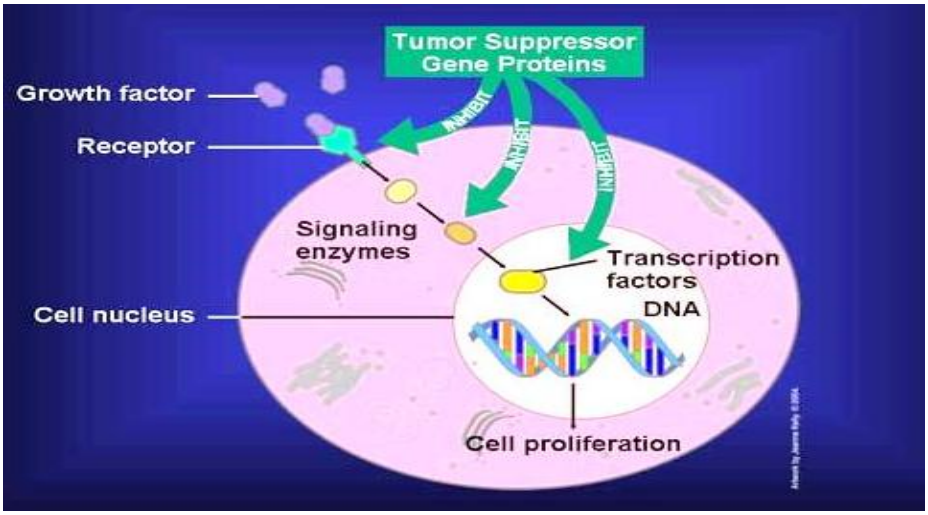

Fig. 1. Tumor suppressor genes act like a brake pedal [National Cancer Institute]

2. PHYSIOLOGICAL ROLES OF TP53

2.1 p53 Family Members: p63 and p73

p63 and p73 are p53-related proteins which possess important functional and structural homologies with p53, specifically in the domain of DNA-binding region. Consisting of conservation of all-important DNA attached residues, p63 and p73 carry the 3 standard domains of a factor used in transcription: the DNA-binding domain (DBD), the carboxyl-terminal oligomerization domain (OD), also amino-terminal transactivation domain (TAD). These two p53 variants take part in cellular responses to stress and development [4]. They carry a number of functional characteristics and work in combination with p53 to monitor tumor genesis. Because of stress signals, they can join p53-target genes and initiate the process of transcription. In the nonappearance of cellular stress, the two forms i.e. p63 and p73 have significant roles in monitoring cellular development and differentiation. The structures of these forms are shown in Fig. 2. Although p63 is essential in the growth of squamous epithelial cells, p73 also involves in neuronal differentiation, and the development of olfactory and nervous system. The family members of p53 are crucial in the growth of inherited abnormalities in humans [5,6]. A firmly regulated vital tumor suppressor p53 is a protein of 53kD weight which switches on in response to changes of normal homeostasis of cell, including nutrient starvation, DNA damage, pH change, virus infection, heat shock, oncogene activation and hypoxia [7]. *TP53* conserves the stability of genome by monitoring different activities, such as programmed cell death, DNA synthesis and repair, cell-cycle arrest and energy metabolism. When stress signals are not available, low levels of p53 protein is present which leads to a finely tuned and dynamic balance between its degradation and its transcription. This equilibrium is of great importance, since excessive p53 can be fatal to cells, while lack of it can cause the development of cancers. p53 protein is strongly monitored in response to different cellular stresses at the phases of protein production i.e. transcription and translation and while different posttranslational modifications are going on, such asacetylation, phosphorylation, adenylation, ubiquitination and methylation [8]. Specifically, the level of p53 is monitored by ubiquitin ligases, for example, Pirh2 and HDM2 (also referred to as MDM2). All these changes regulate the activation of p53 protein, and also its degradation, subcellular localization, the choice of its protein partners, and hence the result of the cellular response after strain: life or death. Particularly, p53 is activated after stress by countless mediators upstream in the route (ATM, ARF, CHK, etc.), stimulating the accumulation of p53 protein because of its repressors inhibition, such as MDM2. p53 is a factor of transcription which binds instantly and specifically as a tetramer of responsive elements of this protein present on DNA to activate or repress the expression of gene [9]. It is known that more than 3,600 target genes are exactly controlled by p53 [10]. Physiologically, p53 stops the proliferation of damaged cells. This concern is of great advantage, as damaged cells are more likely to incorporate mutations, as a result it expresses abnormal growth of cells, which can cause the progression of cancer [11]. It depends on the kind of stress, activated p53 induces either DNA repair or cell-cycle arrest or cell death, but the mechanism controlling the choice between these options has not been explained yet.

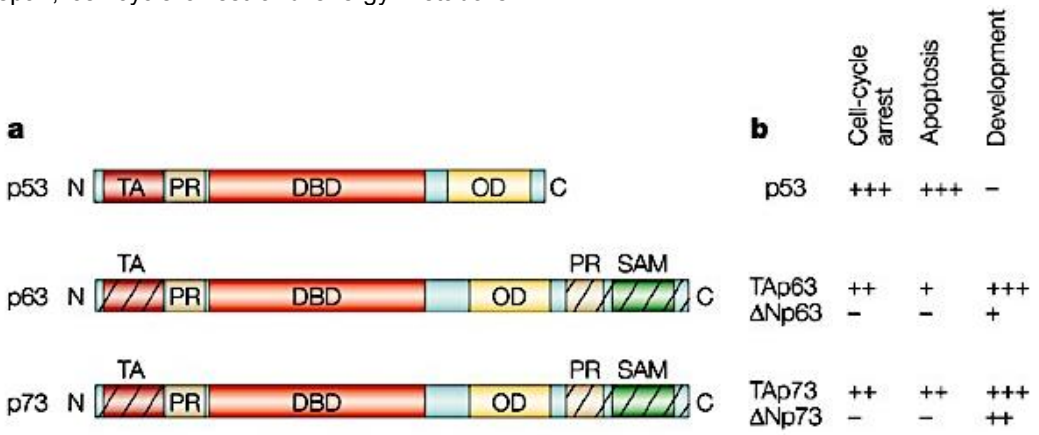

Fig. 2. Structures of p53, p63, and p73 [12]

2.2 p53 Biological Activities as the "Guardian of the Genome"

Once initiated, p53 can stimulate cell-cycle arrest in any of the phases of cell cycle i.e.G1 or G2 phase. As expected, after the DNA damage, p53 stimulates p21, a cyclin dependent kinase inhibitor (Cdk) and moderates cell-cycle arrest at two of the phases of cell cycle i.e. G phase and S phase, permitting DNA repair. Meanwhile, p53 can initiate GADD45 (DNA damage and growth arrest), which controls the arrest of cell cycle in the G/M phases [13]. Alternatively, p53-target genes also take part in cell cycle regulation. In all, the existence of a functional p53 is essential for the dissimilar checkpoints of the cell cycle as it provides the cell time to fixthe damage of DNA [14]. When damage is irreparable, p53 stimulates programmed cell death (apoptosis), and it is believed that p53-associated apoptosis is the foundation of tumor suppression (Fig. 3). A number of genes, which take part in apoptosis, are p53-target genes, specifically in the intrinsic pathway of apoptosis. On contrary, expression of anti-apoptotic proteins, such as Bcl-xL, Bcl-2, or survivin can be repressed by p53. With reference to the extrinsic mechanism pathway of apoptosis, it has been proved that p53 monitors the expression of the death receptors of necrosis associated with apoptosis-stimulating ligand Fas and R2 [15]. Furthermore, it was underlined that p53 can elevate apoptosis in an independent manner of transcription [16]. In reality, after a signal of stress, a region of the cytoplasmic pool of p53 is quickly translocate to mitochondria to enhance the depolarization of mitochondria and hence cells death [17]. Lately, it became known that p53 takes part in other kinds of cell deaths, like necroptosis and autophagy [18].

Roughly, 30 years of experimentation on p53 has revealed that this tumor suppressor regulates many activities in the bodies of living organisms, including cell differentiation, energy metabolism, cell migration, angiogenesis, and embryo implantation [19]. In summary, the literature compiled over the last 34 years shows that p53-associated cell responses to damage are various due to the fact they are acclimatized (proportionately) to the nature, the degree, and the potency of the damage, and also to the cell kind and the initiated oncogenes (e.g. epidermal growth-factor receptor, Ras, estrogen receptor 1). For all that *TP53* is expressed in every cell of the body (excluding erythrocytes), p53 does not force, irrespective of the tissue origin, a ubiquitous cell response to a specified damage. Cells can be different tissue derivatives, and therefore are composed of very diverse molecular components (e.g. lipids, proteins, chromatin structure), which interfere differentially with p53 and hence restrict the activity of p53. It is significant to take the view of biological limitations of a cell in order to comprehend why a p53-associated biological activity is stimulated.

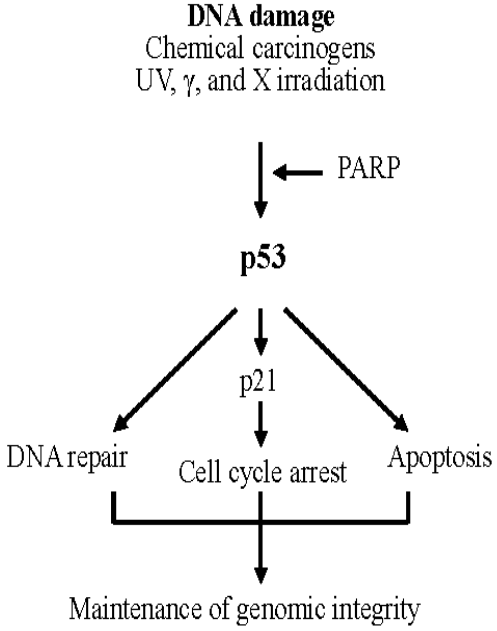

Fig. 3. Role of p53 in cell cycle

2.3 p53 as a Tumor Suppressor in Cancer

In 1979, the p53 protein was discovered for the first time as a protein present in cells, which was overexpressed in cancer cells [20]. Earlier researches had indicated that this protein could enhance cell transformation and proliferation; at first, it was thought to be an oncogene [21]. Nevertheless, in the end of 1980s, various researches have not only uncovered that the studied *TP53* genes carried mutations of missense [22,23] but also wild-type (WT) p53 protein could stop the transformation of cells induced by an oncogene [24]. *TP53* mutations were then underlined in germ-line cells of patients of various cancers. In addition, it has been spotted that mice lacking in *TP53* are susceptible to impulsive tumor genesis. As a result, *TP53* has been distinguished as a tumor-suppressor gene, and is now commonly referred to as "guardian of the genome."

Because of its role in integrating intracellular and extracellular signals to preserve the homeostasis of cell, *TP53* is inoperative in more than 50% of

all the cancers of humans [25,26]. It can also be inoperative at the protein level through interference with cellular/viral proteins, or epigenetic happenings (hyper methylation) of *TP53* [27]. Many surveys have indicated that the pathway of p53 can also be made inoperative through enhanced degradation of p53 (MDM2 overexpression, dysfunction of the Akt pathway, and *PTEN* or *INK4A/ARF* mutation among others), an enhanced nuclear exclusion, or typical behaviors in mechanisms upstream of *TP53* (Chk2 and ATM mutation). Mutations of *TP53* are commonly present in the domain of DNA-binding region, lowering or wholly terminating the role of the protein. Furthermore, recently, p53 mutants have indicated new characteristics, named as "gain of function," which is unique and helps switching on the *TP53* gene on the cellular locations where it is not normally expressed [28].

Repeatedly, *TP53* deletion or mutation is linked with tumor progression, chemotherapeutic failure, metastasis, and a shortened survival. Nonetheless, some kinds of cancer have a low rate of occurrence of *TP53* deletion or mutation (cervical and breast cancer), and this malfunctioning is not always linked with a substandard prognosis. Hence, in such kinds of cancer, the p53 pathway appears to be disarrayed in other manners. Shortly after wards the alterations in the model occurred in the discipline of p53, a few researches served to verify this job of wild-type p53 as a tumor suppressor yet set upp53 protein as most significant participants in oncology. During end of 1960s, numerous ancestries were recognized which were extremely cancer-prone in the Europe and United State. The inherite cancer syndrome referred to as Li-Fraumeni syndrome, an infrequent autosomal condition, which makes the people susceptible to breast cancer and sarcomas [24]. A model mouse with recombinant *TP53* indicated p53-/- as drastically cancer-prone (Fig. 4) [29].

An extensively accepted thing is that mutations of *TP53* are the commonest genetic occurrences in tumors of human [30,31]. The function of wild type *TP53* is changed by various mechanisms, such as many different DNA tumor viruses inhibit p53, adenovirus E1B-55-kDa protein and SV40 large T-antigen are their examples [32]. HPV types 16 and 18 gets affected in cervical cancer, this reveals a biological connection [33]. Up-regulation of negative regulators or their activation can cause the tumors to inactivate *TP53*. An E3 ubiquitin ligase (Mdm2) is the chief negative regulator, which normally keeps the concentration of p53 under control [34]. Moreover, a homolog of MdmX/Mdm4 and Mdm2, sometimes works as a negative regulator for*TP53* [35] expectedly, both these negative regulators are overexpressed in various neoplasms [36]. Now we can say, wild type*TP53* has a crucial role in oncology.

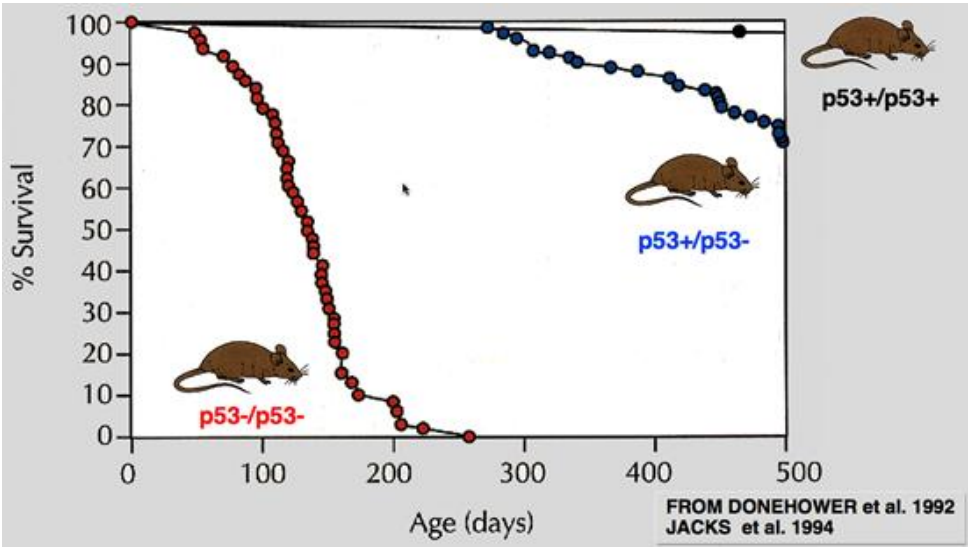

Fig. 4. Mice deficient in p53 are prone to develop cancer [37]

3. GERMLINE TP53 MUTATIONS AND INHERITED CANCER PREDISPOSITION

Germ line mutations in the tumor suppressor gene of *TP53* are linked with the Li-Fraumenimulti-cancer predisposition syndrome (LFS). This autosomal dominant syndrome is distinguished by a high occurrence of an early-onset tumors consisting mainly of sarcoma, breast cancer, leukemia, adrenocortical carcinoma (ACC), and brain tumors. The uniformity between natures of cancers developed in patients with clinical attributes of LFS, and those with the highest frequency of mutations in somatic cells of TP53 were involved in the identification of inherited *TP53* mutations as the foundation for this syndrome. Diagnostic trials for germ line*TP53* mutations in various families with suspected Li-Fraumeni Syndrome through direct sequencing of DNA exons 2 – 11 has now been confirmed in a large clinical unit [38]. From that research, it has been put forward that childhood ACC and the existence of a family member with one of the basic cancers, brain tumor, sarcoma, breast cancer, or ACC, are the most likely measures of a germ line *TP53* mutation that should induce an appeal for diagnostic testing by molecular screening.

A thorough analysis of *TP53* mutation types in a great cohort of French LFS families has accepted that missense mutations are recurrent and are linked with earlier inception of tumor as comparable with loss-of-function mutations [39]. Even such missense mutations were considered transcriptionally inactive based on yeast functional assays, their connection with earlier emergence of tumors asserts in service of an extra gain-of-function oncogenic consequence [38]. In conditions of the distribution of codon along the molecule of p53, germ line mutations carry out a similar scheme to somatic mutations in sporadic cancers, with hotspot mutations being connected chiefly with the DNA binding domain. One noteworthy exception is the increased rate of the mutations of codon 337 in LFS families. Single base-pair replacements at Arg337 have been reported in 233 individuals and 72 families with LFS, but are exceptionally infrequent in sporadic cancers (0.1% single base-pair substitutions). The R337H mutation prominently present in LFS families from the regions of Brazil, is a risk allele for ACC (pediatric) and is a distinctive example of tissue-specific vulnerable mutation [39].

4. MUTANT p53 SIGNALING

One of the most frequent genetic changes in the tumors that occur in humans is the mutation of the p53 gene. Almost all of the p53 mutations are present within the central domain of DNA-binding region (residues 102–292) and a small number of hot spots are present in the conserved regions of the gene. Despite the fact loss of p53, expression has been noticed in different cancers; almost all of the p53 mutations culminate in expression of mutant p53 that displays gain-of-function properties. Such changes diligently promote tumor genesis and pro-survival signals, unrelated to the loss of wild-type p53 function [40,41]. *TP53* is present at the crossroads of a system of signaling pathways that are essential for the regulation of apoptosis initiated by genotoxic and non-genotoxic stresses and the cell growth [4]. In normal cells, the concentration of *TP53* protein is down regulated through the binding of proteins like PIRH2, MDM2, JNK, or COP1 that play a part in the degradation of *TP53* by means of the ubiquitin / proteasome pathway. Although majority of other genes are regulated by *TP53*, this initiates a loop regulation, which keeps the concentration of *TP53* very low in unstressed normal cells. After genotoxic or non-genotoxic stresses, *TP53* initiates in a two phases. In the first stage, protein *TP53*concentration is enhanced in the cells through the inhibition when it communicates with mdm2, which is a negative regulator. Over translation of *TP53* RNA makes the accumulation of *TP53* certain. In the second stage, a chain of modulators (kinases, acetylases) starts the transcriptional activity of *TP53* [2]. Downstream signaling comprises of a large series of genes, which are switched on by the trans-activating attribute of *TP53*. This happens when particular DNA of the *TP53* protein joins with a *TP53* response factor (*TP53* RE) that is found either in the promoter or introns of required genes. There are different varieties of physiological processes, which involve *TP53*; the most studied is its role in tumor-suppression. *TP53* incorporates cell signaling from damaged subcellular organelles, additionally extracellular matrix, cell– cell contact, cytokines, hormones and nutrient level. On the basis of these signals, *TP53* plays a part in the decision of cell-fate to activate differentiation, cell survival, cell migration, senescence, or programmed cell death. Despite that, the fundamental molecular mechanisms are still uncertain. Moreover, different technical advances in genetics and biochemistry cause different studies to highlight that the *TP53* gene encodes

various *TP53* protein isoforms, which work together with *TP53* and regulate its activity towards either promoting cell death or survival.

5. APOPTOSIS AND CARCINOGENESIS

Cancer happens when chain of genetic modifications occur in the course of time. When the alteration of normal cell into malignant occurs, the thing which stops the death of the cell is cancer [42]. In the early 1970s, a study connected apoptosis with the removal of tumor cells, tumor progression, and hyperplasia [43]. Therefore, reduced apoptosis has an important role in cancer. TP53, which is encoded by its tumor suppressor gene, is present at the tiny arm of 17th chromosome (17p13.1). The molecular weight of TP53 is 53kDa so it is named after it [25]. In 1979, p53 was for the first time spotted as weakly oncogenic. Eventually it was referred to as “gain of oncogenic function” [44]. With it emergence, many researchers found that p53 not just has a role in stimulation of apoptosis but also plays a part in the regulation of cell cycle, gene amplification, differentiation, and segregation of chromosomes [29] and is referred as the “guardian of the genome” [39]. Researchers informed that some of the target genes of p53 which are in the players of cell cycle regulation and apoptosis are abnormally expressed in the cells of melanoma, resulting in the aberrant activity of p53 and playing a part in the proliferation of these cells [30] In a model of mouse with an N-terminal deletion mutant of p53 (Δ122p53) that correlates to the Δ133p53, researchers also showed that these mouse had reduced survival, more aggressive and different tumor spectrum, a marked proliferative benefit on cells, decreased apoptosis and a complex pro-inflammatory phenotype [45].

6. MARKING p53

Numerous p53-based programs have been studied for the cure of cancer. Normally, these are divided into three major classes: 1) gene therapy 2) drug therapy 3) immunotherapy.

6.1 p53 Based Gene Therapy

Since 1979, p53 has remained an important protein in the cancer-based research. Almost all the cellular responses in the body like differentiation, genotoxic stress, apoptosis and senescence are mediated by p53. Many hypotheses are driven by the targeting pathways of p53, which play an essential role in the treatment and drug designing of cancer [46]. In 1996, when the first report of p53 gene therapy was inquired, tumor cells obtained from the lung cancer were treated with the retroviral vector and the impact of p53 in the progression of cancer was studied. This practice showed the feasibility of p53-based gene therapy [42]. It was found that removal of the tumor genes is not the ultimate function of the p53 rather p53-based gene therapy is a breakthrough in the researches of cancer progression. Different studies were conducted on the p53 gene to sensitize cancer cells of neck and head, prostate colorectal cancer, and glioma, which acquired malignancy because of ionizing radiation [43]. Even a number of researches have passed the phase III clinical experiments, yet no approval from the FDA has been granted [44]. The use of genetically modified viruses to screen out the cells, which lack the p53, is another fascinating p53 gene-based program. An example of it, which came into light, is the oncolytic adenovirus, which was genetically modified with itsE1B 55kDa gene removed. It provided a chance to the virus to selectively lyse and duplicate in the cancer cells which lack p53 [47].

6.2 p53 Based Drug Therapy

Various mechanisms were used to study the effect of different drugs on the infected p53. One of the drugs used for this purpose is referred to as small molecules that help in returning the abnormal cells of p53 back to the normal. Phikan083, a derivative of carbazole and small molecule is its example. It binds to the mutant p53 and return it into normal state. Another example is CP-31398, which inserts, destabilizes, and then changes the core domain complex of p53DNA; consequently, it leads to the repair of unsteady molecule of p53 mutants [42]. Some other drugs, which can be used to mark p53, are MI-219, tenovin, and the nutlins. Structure of nutlins resembles to the cis-imidazoline that stop the interaction of MDM2 and p53, selectively initiate senescence in cancer cells and stabilize p53 at the same time. MI-219 distorts the interaction between MDM2 and p53, hence prevents the selective apoptosis in cancer cells, cell proliferation, and inhibition of tumor growth. Meanwhile, the tenovins small molecules, which activate p53, have been indicated to reduce the in vivo growth of tumor [47].

7. CONCLUSION

As *TP53* gene instructs the cell to form Tumor suppressor protein p53, which keeps the cell division normally regulated, it prevents the tumor formation. Any mutation in the gene eventually disrupts the normal functioning of the protein, resulting in the formation of various kinds of tumor like breast cancer, Li-Fraumeni syndrome. Hence, it would not be wrong to say that drug-based and gene therapies are capable of treating the cancers occurdue to *TP53*mutations.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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