

Review Article

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

ABSTRACT

The *TP53* gene is a tumor suppressor gene that its action inhibits the emergence of cancerous growth. The signaling of *TP53* takes part in the co-ordination of the cellular response to various kinds of stress like hypoxia and DNA damage. The downstream signals begin multiple processes such as senescence, apoptosis and the arrest of cell cycle. In the case of tumor growth, inactivation of *TP53* occurs. According to estimation, more than half of all cancers imply the inactivating mutations of *TP53*, which leads to the expression of mutant *TP53* protein. An extensive range of cancers carry the mutations of *TP53* or certain other defects which deregulate *TP53* 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. Within the cell, as *TP53* protein binds DNA, it triggers another gene to synthesize a protein named *TP21*, which interferes with a cell division-stimulating protein (cdk2). When *TP21* forms a complex with cdk2 the cell cannot pass onto the next phase of cell division. Therefore, Mutant *TP53* can no longer get itself attached to DNA effectively, and as a result, the *TP21* 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 *TP53* is also given the name “guardian of the genome”, due to its part in maintaining genetic stability and preventing the formation of tumors. After the cell injury when *TP53* 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 eventually occurrence of cancer takes place [2]. Tumor suppressor gene *TP53* is a component of transcription, which controls the cell cycle. *TP53* turns on the proteins, which repair DNA but when DNA has prolonged damage, it halts the cycle of the cell at the G1/S phase on the recognition of DNA damage, and can initiate apoptosis if DNA damage turns out to be irreversible. Carcinogenesis takes place if this system goes out of control. *TP53* gene works resembling brake pedal of a car. Normally, it retains the cell from multiplying excessively fast, similar to how a brake stops car from moving speedily. When there is some mutation in the gene, division of the cell becomes out of control.

If someone receives just a single copy of functional *TP53* gene from the biological father and mother, 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 in which caspase (enzyme) activation plays a chief role [3]. *TP53* is a crucial suppressor protein in apoptotic pathways. *TP53* is located at the crossroads of a system of signaling mechanisms, which are important to keep the apoptosis and cell growth regulated initiated by non-genotoxic and genotoxic stresses [4]. *TP53* is a tumor suppressor gene, which corrects DNA mistakes, declines the cell division, or inform cells when to die (a process referred as *programmed cell death* or *apoptosis*) [3]. When *TP53* genes don't function appropriately, growth of the cells become impossible to manage, which can lead to tumor formation. *BRCA1*, *BRCA2*, *RB1*, and *APC* is some other tumor suppressor protein. The malfunctioning of *TP53* results in enhanced tumor growth because of reduced apoptosis [3]. *TP53* gene works similar to the brake pedal of a car (Fig. 1).

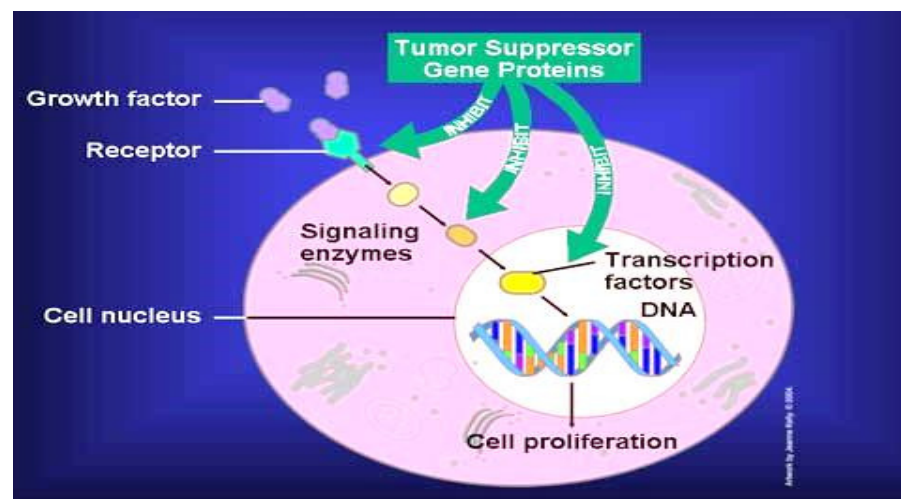


Fig. 1. Tumor suppressor genes act like a brake pedal.

2. PHYSIOLOGICAL ROLES OF TP53

2.1 TP53 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 development and stress [5]. They own a number of functional characteristics and work in combination with p53 to monitor tumorigenesis. As a result 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 the monitoring of 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 [6]. Principally, not only the unique roles of each member of p53 family but also their interference with one another are critical for tumor suppression [7]. A firmly regulated vital tumor suppressor p53 is a protein of 53 kD weight which turns 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 [8]. p53 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 because of this a finely tuned and dynamic balance exists between its degradation and its transcription. This equilibrium is of great importance, since excessive p53 can be fatal to cells, on the other hand 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 as acetylation, phosphorylation, neddylation, ubiquitination, methylation and sumoylation [9]. Specifically, the level of p53 is monitored by ubiquitin ligases, for example, Pirh2 and HDM2 (also referred to as MDM2). All those 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 p53 present on DNA to activate or repress the expression of gene [10]. It is known that more than 3,600 target genes are exactly controlled by p53 [11]. 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 express abnormal growth of cells, which can cause the progression of cancer [12]. 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.

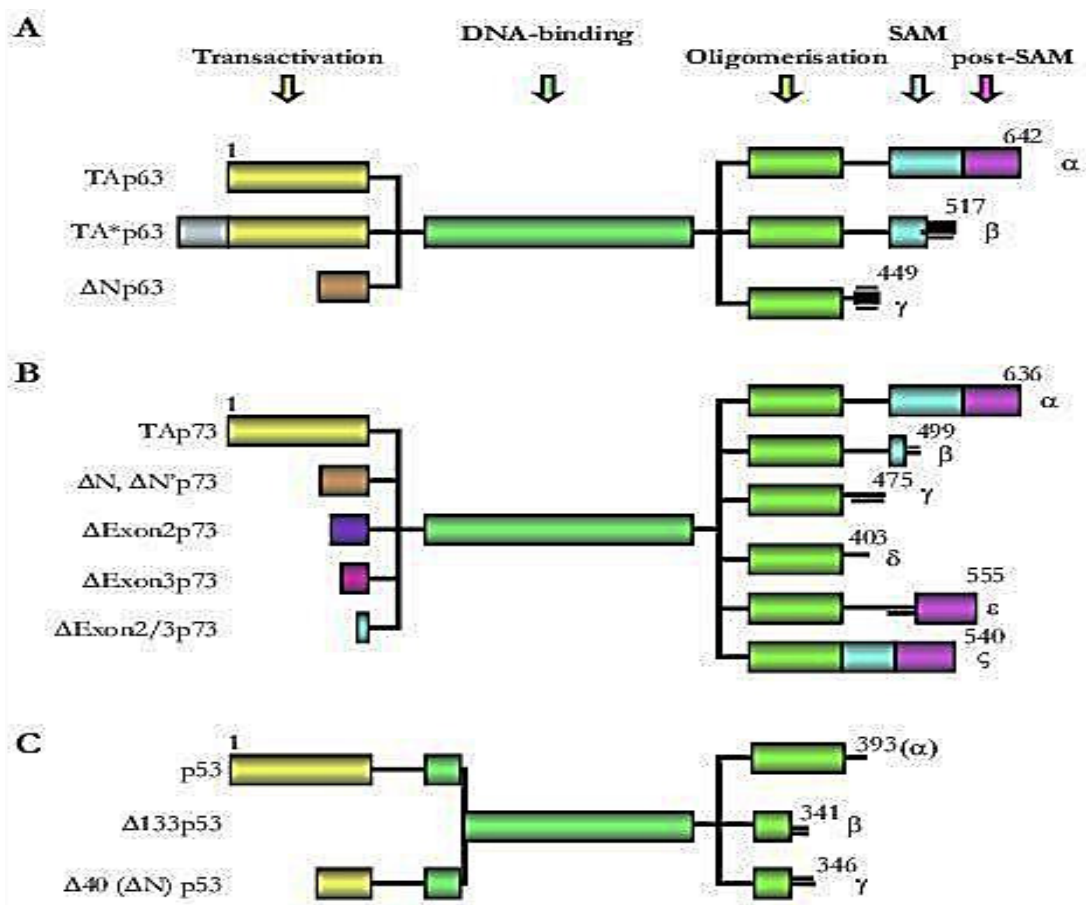


Fig. 2. Structures of p53, p63, and p73

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 kinase inhibitor that depends on cyclin (cyclin-dependent kinase Cdk) and moderates cell-cycle arrest at two of the phases of cell cycle i.e. G and S phases, 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]. Alternative p53-target genes also took part in cell-cycle regulation encompass 14-3-3 and the miR-34a proteins. In all, the existence of a functional p53 is essential for the dissimilar checkpoints of the cell cycle, as a result of that giving the cells time to fix the 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 mechanism pathway of apoptosis. On contrary, antiapoptotic proteins expression, 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 factor-associated 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 translocated to

mitochondria to enhance the depolarization of mitochondria and hence cell death [17]. Lately, it became known that p53 takes part in other kinds of cell death, 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 p53 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 interface 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.

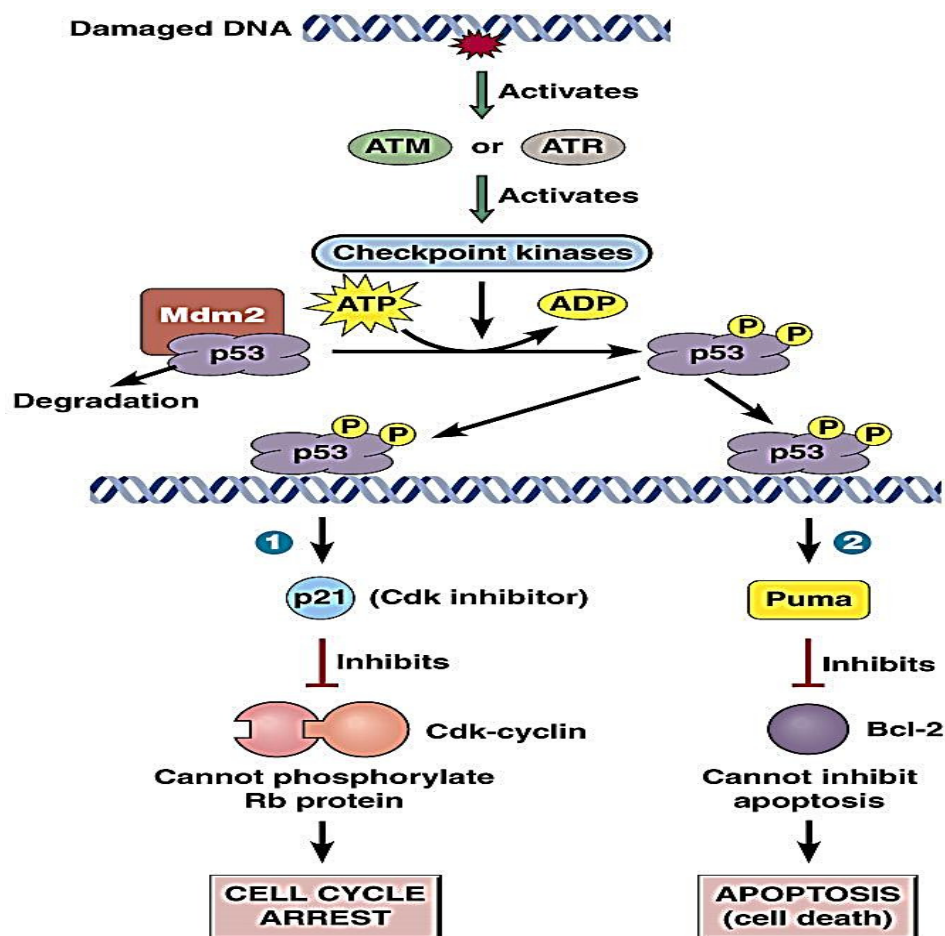


Fig. 3. Role of p53 in cell cycle

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 Li-Fraumeni syndrome [25] and in plenty of other cancer cells. In addition, it has been spotted that mice lacking in *TP53* are susceptible to impulsivetumorigenesis. As a result *TP53* has been

distinguished as a tumor-suppressor gene, and is now commonly referred to as “guardian of the genome”.

All the occurrences, which are likely to encourage the formation of cancer cells, like oncogene activation, abnormal proliferation, DNA damage, or an irregular cell cycle, cause the activation of p53. This tumor suppressor prevents the proliferation of damaged cells, stimulates cell death, and hence stops the formation of cancer. Because of its role in integrating intracellular and extracellular signals to preserve the homeostasis of cell, p53 is inoperative in more than 50% of all the cancers of humans [26] [27]. It can also be inoperative at the protein level through interference with cellular/viral proteins, or epigenetic happenings (hypermethylation) of *TP53* [28]. 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 atypical behaviors in mechanisms upstream of p53 (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 are unique from those of p53 [29]. 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 afterward, 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 up p53 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 inherited cancer syndromes referred to as Li-Fraumeni syndrome, an infrequent autosomal condition, which makes the people susceptible to breast cancer and sarcomas [25]. A model mouse whose p53 was because of recombination of homologues indicated even p53^{-/-} mouse were common, they were drastically cancer-prone (Fig. 4) [30].

An extensively accepted thing is that mutations of p53 are the commonest genetic occurrences in tumors of human [31]. In fact, it has been found that the alterations in the function of p53 occur in many tumors of human [32]. The function of wild type p53 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 [31]. 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 p53. 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 p53 [35]. Expectedly, both these negative regulators are overexpressed in various neoplasms [36]. Now we can say, wild type p53 has a crucial role in oncology.

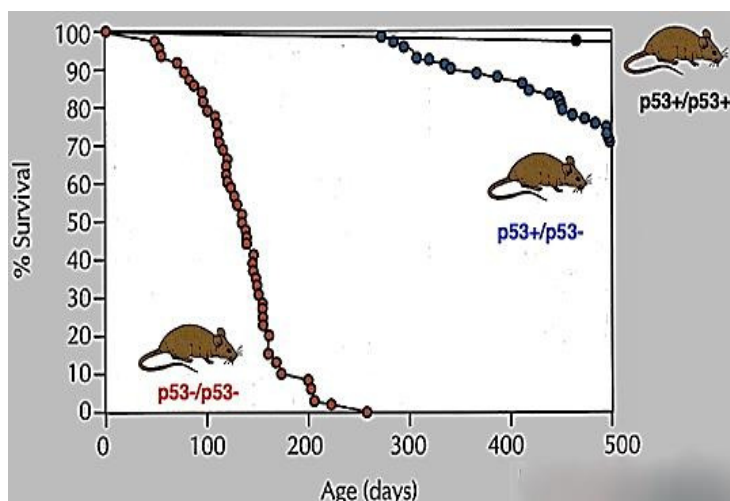


Fig. 4. Mice deficient in p53 are prone to develop cancer.

3. GERMLINE TP53 MUTATIONS AND INHERITED CANCER PREDISPOSITION

Germline mutations in the tumor suppressor gene of TP53 are linked with the Li-Fraumeni multiscancer predisposition syndrome (LFS). This autosomal dominant syndrome is distinguished by a high occurrence of 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 [37]. 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 the most recurrent and are linked with earlier inception of tumor as comparable with loss-of-function mutations [38]. Even such missense mutations were considered to be transcriptionally inactive on the basis of yeast functional assays, their connection with earlier emergence of tumors asserts in service of an extra gain-of-function oncogenic consequence [39]. 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 [40].

4. TP53 ABNORMALITIES AND BIOMARKERS OF CANCER PROGNOSIS

A large number of backdated researches have linked abnormal p53 protein expression as well as mutation in somatic cells with lack of response to therapy or substandard survival. However, the clinical importance of p53 position for patient result has been [41] and keeps on to be one of the most contentions of p53 research. The problem mainly originates from the inborn complexity of the p53 mechanism pathway, the abundance of mutations in various cancer types and clinical phases, and their contrasting effects, as well as absence of randomized potential researches compounded by heterogeneity in sample types, experimental designs, and techniques. Furthermore, it would possibly be naïve to presume that all over the place mutated gene would have the same clinical importance regardless of circumstances (Fig. 5). There have been promising findings with respect to the survival prediction by TP53 mutations. For tumors of the head and neck, breast, liver, lymphoid systems, and hematopoietic, a majority of researches depict a connection of TP53 mutation with worsened survival. For tumors of the brain, bladder, lung, esophagus, colon, and ovary, about as many researches found a link as did not. For tumors of the prostate gland, pancreas, stomach, and rectum, the number of patients in the respective units reported was small. The largest patient units have been diagnosed for colorectal and breast carcinomas.

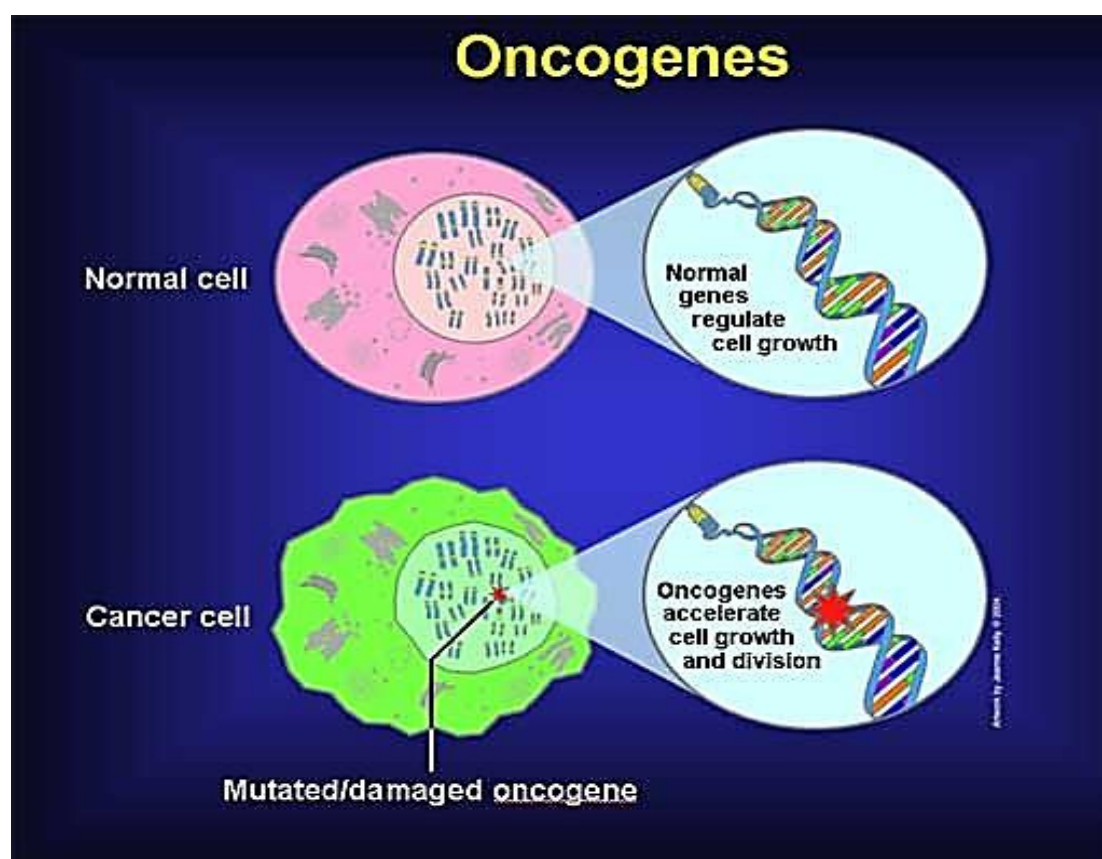


Fig. 5. Normal and Cancer cells.

4.1 Colorectal Cancer

Two large meta-analysis cases on the estimated value of p53 abnormalities on result of colon cancer depict opposite results with respect to the response of chemotherapy, but crucially similar lack of important effect on survival prediction [42]. On the other hand, a sequencing-based, potential study on primary operable colorectal cancer patients facing respective surgery indicated that particular TP53 mutations were linked with worse prognosis [43]. Likewise, a branch of functionally inoperative mutations predicted substandard survival in late phase of colorectal cancers [44].

4.2 Breast Cancer

Scientists have found numerous tumor suppressor genes, and some have been linked with enhanced risk of breast cancer. There are two types of tumor suppressor genes i.e. BRCA1 (Breast Cancer-1) and BRCA2, which are mutated, in an excessive percentage of early-onset (before the age of 45) inherited ovarian cancer cases and breast cancer. Researchers are just starting to find out how these genes work, and how often mutations in these genes take place in females with predisposition of breast cancer. One latest research found that Ashkenazi Jewish descent females with mutation in BRCA1 or BRCA2 had just more than 50% possibility of developing breast cancer by the age of 70. This is a reduced number than predicted by earlier cases. Much more experimentation is required to control the risk of breast cancer linked with inheriting mutations in these genes. Either the p53 tumor suppressor gene does not work or is missing in more than 60% of all the patients of breast cancers. The p53 gene has a critical part in the DNA damage response to the cell. We have already elucidated the significance of the p53 protein in the job of inducing mutated cells to carry out cell suicide, and its part in "braking" the cell cycle to stop the cells with DNA damage from dividing anymore. In most studies, damage to the p53 gene is obtained during one's lifetime, despite of the fact in few instances a trend of early-onset tumors has been tacked down to inheriting genes of mutated p53 (<100 families across the world with Li-Fraumeni-Syndrome). Breast cancer appears to exhibit the explicit link of TP53 mutation with substandard survival in prospective, large, sequence-based researches. The

existences of TP53 mutation was a self-sufficient predictor of cancer-specific death in a large unit of females with primary breast cancer and linked with substandard predictions when associated with the absence of receptor of progesterone [45].

The general image which is appearing from breast cancer shows that missense mutations which affect binding of DNA are specifically deleterious and are linked with the worse survival, in contrast null mutations or non missense mutations in the DNA-bindings motifs are linked with in-between reduction of survival matched up with no mutations [46]. In addition to it a large prospective study shows TP53 mutation was identified to be linked with substandard survival as well as “ERBB2p” and “basal-like” gene expression subgroup, which they had high death rate [47]. Missense TP53 mutations also bestowed on greater risk of death and recurrence in contrast to the wild-type TP53 in females with node-negative breast tumors [48]. In comparison to the analysis of TP53 mutations, the overall clinical importance of p53 immunostaining in breast tumor is substandard in regard to other clinical parameters, comprising Her-2 positivity [49]. Consequently, the daily use of p53 immuno-staining is not advised in clinical practice [50].

4.3 Head and Neck Cancers

A potential, multicenter experiment analyzed TP53 mutation condition in squamous-cell carcinoma of the neck and head through p53 GeneChip and spotted that existence of any TP53 mutation had some unfavorable effect on survival, but those mutation that were the outcomes of disrupted binding of DNA led to an even worse prediction [21]. In correspondence, TP53 mutations in direct DNA contact regions ended in rapid tumor progression and decreased therapeutic responsiveness in neck and head squamous cell carcinoma [22]. Moreover, the expression of p53 in head and neck and its demographic data is shown in Table 1.

		P53 expressions		References	
Variables	Categories	(+)	(-)		
Sex	Male	26	25	p= 0.51	(Angela <i>et al.</i> , 1997)
	Female	4	7		
Race	White	28	30	p= 1.00	
	Asian	1	0		
	Black	1	1		
Age	< 45	4	5	p= 0.89	
	46-60	13	12		
	> 60	13	15		
Family history	Present	24	23	p= 0.45	
	Absent	6	9		
Smoking habit	Present	26	25	p= 0.42	
	Absent	2			
Alcoholism	Present	6	8	p= 0.48	
	Absent	22	9		

Table 1. Results of a research carried out to find the relation between p53 expression and demographic data

4.4 Lung Cancer

Survival was higher among the patients with stage I NSCLC, with wild-type p53 than in those with

mutant p53 [23], but TP53 mutations were not linked with the restricted survival of cases with advanced-stage NSCLC [44]. Nevertheless, TP53 mutations were found importantly connected with recurrence of NSCLC [45].

4.5 Prostate Cancer

Divergent expression of p53 in prostate cancer was related to increased risk of disease-specific death and also with the growth of distant metastasis at the age of 5 years [46]. Essentially one of the studies provided support for using p53 as a marker to arrange or classify patients experiencing radiotherapy and androgen deprivation; by showing that long-term androgen deprivation may importantly ameliorate the cause-specific survival for those with divergent p53 [46].

5. APOPTOSIS AND CARCINOGENESIS

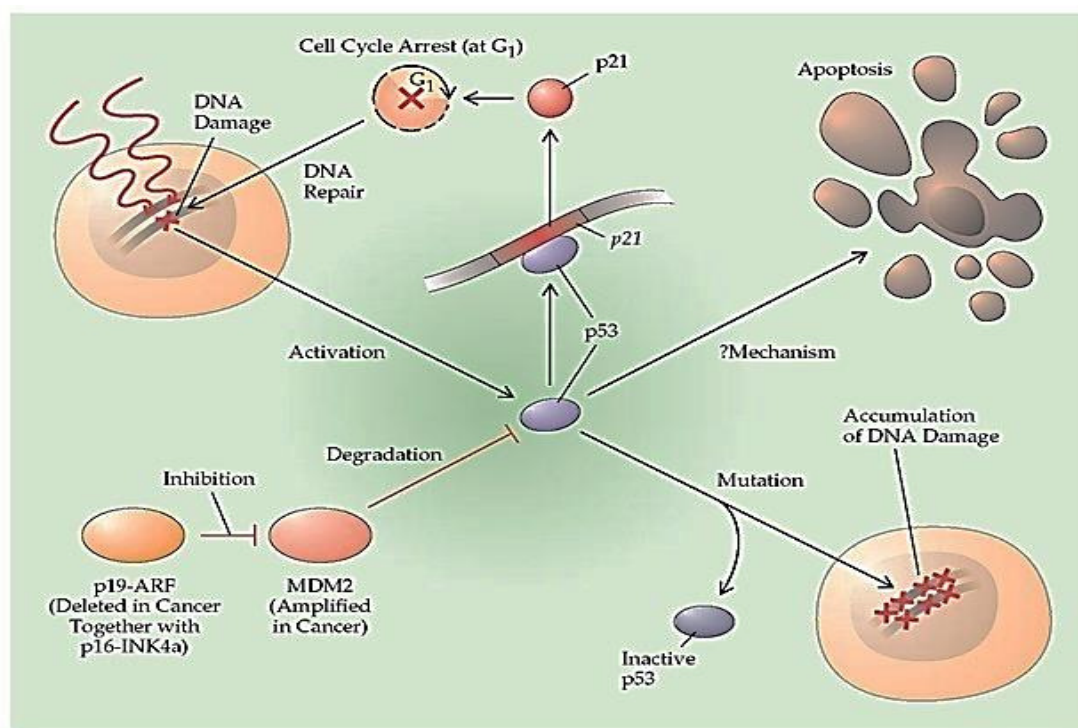


Fig. 6. Apoptosis and Cell Cycle Arrest

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 [37]. In the early 1970s, a study connected apoptosis with the removal of tumor cells, tumor progression and hyperplasia [38]. 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 [26]. In 1979, p53 was for the first time spotted as weakly oncogenic. Eventually it was referred to as “gain of oncogenic function” [50]. With its 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 [40] and is referred to as the “guardian of the genome” [30]. Lately, Avery-Kieida et al. 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 [31] (Fig. 6). In a model of mouse with an N-terminal deletion mutant of p53 ($\Delta 122$ p53) that correlates to the $\Delta 133$ p53, Slatter et al. showed that these mice had reduced survival, more aggressive and different tumor spectrum, a marked proliferative benefit on cells, decreased apoptosis and a complex proinflammatory phenotype [32].

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 and 3) immunotherapy.

6.1 p53 Based Gene Therapy

1

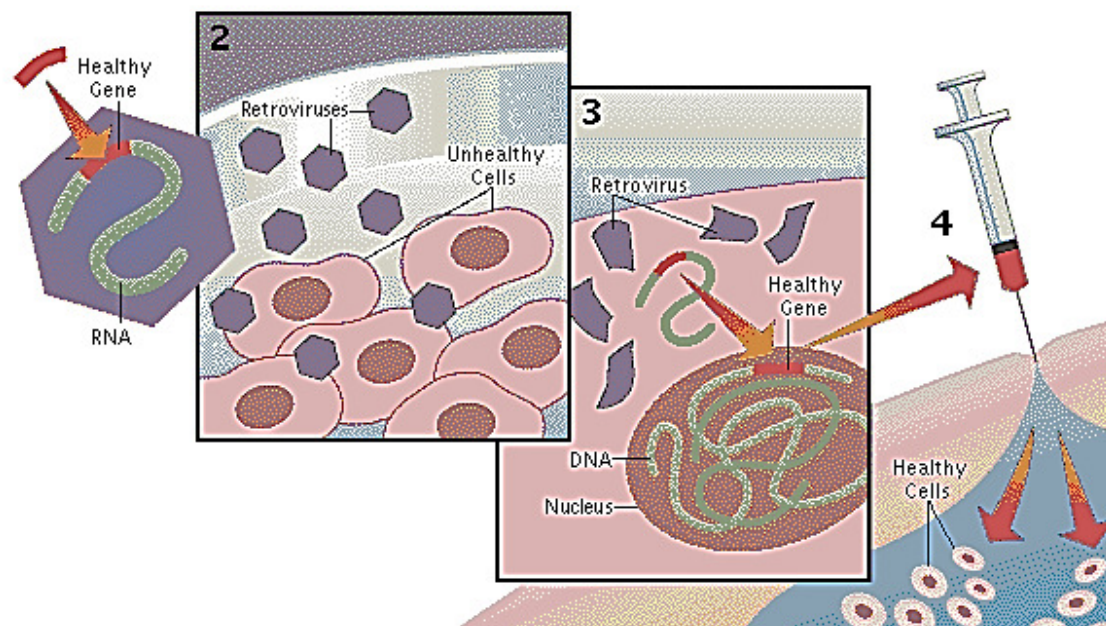


Fig. 7. p53 based gene therapy

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 [43] (Fig. 7). 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 cancers and colorectal and glioma which acquired malignancy because of ionizing radiation [44]. Even a number of researches have passed the phase III clinical experiments, yet no approval from the FDA has been granted [45]. 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 its E1B-55 kDa gene removed. It provided a chance to the virus to selectively lyse and duplicate in the cancer cells which lack p53 [46].

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 p53 DNA; consequently it leads to the repair of the unstable molecule of p53 mutants [47]. 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 stops the interaction of MDM2 and p53, selectively initiate senescence in cancer cells and stabilize p53 [48] 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, are small molecules which activate p53, which have been indicated to reduce the in vivo growth of tumor growth [49].

7. 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 tumorigenesis and pro-survival signals, unrelated to the loss of wild-type p53 function [49][50]. *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 (William & Prives, 2012). In normal cells, the concentration of *TP53* protein is downregulated 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 [4]. 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. Overtranslation 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 transactivating attribute of *TP53*. This happens when particular DNA of the *TP53* protein joins with a *TP53* response factor (*TP53* RE) which is found either in the promoter or introns of required genes [4].

8. CONCLUSION

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.

REFERENCES

1. Surget, S., Khoury, M. P., Bourdon, J. C. Uncovering the role of p53 splice variants in human malignancies: a clinical perspective. *OncoTargets and Therapy*. 2013;20(14):59-60.
2. Razmik, M., Andrais, B., Scott, A., Murray, D. New insights into p53 Signaling and Cancer Response to Damage DNA. *J Biomed Biotechnol*. 2012;17(3):16-25
3. Elmore, S. Apoptosis: a review of programmed cell death. *Toxicologic Pathology*. 2007;35(4):495-516.
4. William, A., Prives, C. Mutant p53. *Genes Develop*. 2012;26:1268-128.
5. Murray-Zmijewski, F., Lane, D. P., Bourdon, J. C. p53/p63/p73 Isoforms: an orchestra of isoforms to harmonize cell differentiation and response to stress. *Cell Death Differ*. 2006;13(6):962-972.
6. Dötsch, V., Bernassola, F., Coutandin, D., Candi, E., Melino, G. p63 and p73, the ancestors of p53. *Cold Spring Harbor Perspect Biol*. 2010;2(9): 48-87.
7. Flores, E. R., Sengupta, S., Miller, J. B. Tumor predisposition in mice mutant for p63 and p73: evidence for broader tumor suppressor functions for the p53 family. *Cancer Cell*. 2005;7(4): 363-373.
8. Oren, M. Decision making by p53: life, death and cancer. *Cell Death Differ*. 2003;10(4):431-442.
9. Meek, D. W., Anderson, C. W. Posttranslational modification of p53: cooperative integrators of function. *Cold SprHarbPersp Biol*. 2009;1(6):09-50.
10. Funk, W. D., Pak, D. T., Karas, R. H., Wright, W. E., Shay, J. W. A transcriptionally

- active DNA-binding site for human p53 protein complexes. *Mol Cell Biol.* 1992;12(6):2866-2871.
11. Li, M., He, Y., Dubois, W., Wu, X., Shi, J., Huang, J. Distinct regulatory mechanisms and functions for p53-activated and p53-repressed DNA damage response genes in embryonic stem cells. *Mol Cell.* 2012;46(1):30-42.
12. Hall, P. A., McKee, P. H., Menage, H. D., Dover, R., Lane DP. High levels of p53 protein in UV-irradiated normal human skin. *Oncogene.* 1993;8(1):203-207.
13. Taylor, W. R., Stark, G. R. Regulation of the G2/M transition by p53. *Oncogene.* 2001;20(15):1803-1815.
14. Sperka, T., Wang, J., Rudolph, K. L. DNA damage checkpoints in stem cells, ageing and cancer. *Nature Review Mol Cell Biol.* 2012;13(9): 579-590.
15. Owen-Schaub, L. B., Zhang, W., Cusack, J. C. Wild-type human p53 and a temperature-sensitive mutant induce Fas/APO-1 expression. *Mol Cell Biol.* 1995;15(6): 3032-3040.
16. Moll, U. M., Wolff, S., Speidel, D., Deppert, W. Transcription-independent pro-apoptotic functions of p53. *Current Opin Cell Biol.* 2005;17(6):631-636.
17. Mihara, M., Erster, S., Zaika, A. p53 Has a direct apoptogenic role at the mitochondria. *Mol Cell.* 2003;11(3):577-590.
18. Crighton, D., Wilkinson, S., O'Prey, J. A p53-induced modulator of autophagy, is critical for apoptosis. *Cell.* 2006;126(1):121-134.
19. Maddocks, O. D., Vousden, K. H. Metabolic regulation by p53. *J Mol Med.* 2011;89(3):237-245.
20. Lane, D. P., Crawford, L. V. T antigen is bound to a host protein in SV40-transformed cells. *Nature.* 1979;278:261-263.
21. Reich, N. C., Levine, A. J. Growth regulation of a cellular tumor antigen, p53, in non-transformed cells. *Nature.* 1984;308(5955):199-201.
22. Mowat, M., Cheng, A., Kimura, N., Bernstein, A., Benchimol, S. Rearrangements of the cellular p53 gene in erythroleukaemic cells transformed by Friend virus. *Nature.* 1985;314(6012):633-636.
23. Munroe, D. G., Rovinski, B., Bernstein, A., Benchimol, S. Loss of a highly conserved domain on p53 as a result of gene deletion during Friend virus-induced erythroleukemia. *Oncogene.* 1988;2(6):621-624.
24. Hinds, P., Finlay, C., Levine, A. J. Mutation is required to activate the p53 gene for cooperation with the ras oncogene and transformation. *J Virol.* 1989;63(2):739-746.
25. Srivastava, S., Zou, Z. Q., Pirollo, K., Blattner, W., Chang, E. H. Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. *Nature.* 1990;348(6303):747-749.
26. Levine, A. J., Momand, J., Finlay, C. A. The p53 tumor suppressor gene. *Nature.* 1991;351(6326):453-456.
27. Hollstein, M., Sidransky, D., Vogelstein, B., Harris, C. C. p53 mutations in human cancers. *Science.* 1991;253(5015):49-53.
28. Levine, A. J., Oren, M. The first 30 years of p53: Growing ever more complex. *Nature Rev Cancer.* 2009;9:749-758.
29. Goldstein, I., Marcel, V., Olivier, M., Oren, M., Rotter, V., Hainaut, P. Understanding wild-type and mutant p53 activities in human cancer: new landmarks on the way to targeted therapies. *Cancer Gene Ther.* 2011; 18(1):2-11.
30. Attardi, L. D., Jacks T. The role of p53 in tumor suppression: Lessons from mouse models. *Cell Mol Life Sci.* 1999;55: 48-63.
31. Levine, A. J. The common mechanisms of transformation by the small DNA tumor viruses: The inactivation of tumor suppressor gene products: p53. *Virol.*

- 2009;384:285-293.
32. Polager, S., Ginsberg, D. p53 and E2f: Partners in life and death. *Nature Rev Cancer*. 2009;9:738-748.
33. Ferenczy, A., Franco, E. Persistent human papillomavirus infection and cervical neoplasia. *Lancet Oncology*. 2002;3: 11-16.
34. Manfredi, J. J. The Mdm2–p53 relationship evolves: Mdm2 swings both ways as an oncogene and a tumor suppressor. *Genes Devel*. 2010;24:1580-1589.
35. Marine, J. C., Dyer, M. A., Jochemsen, A. G. MDMX: From bench to bedside. *J Cell Sci*. 2007;120:371-378.
36. Marine, J. C., Francoz, S., Maetens, M., Wahl, G., Toledo, F., Lozano, G. Keeping p53 in check: Essential and synergistic functions of Mdm2 and Mdm4. *Cell Death Differ*. 2006;13:927-934.
37. Gonzalez, K. D., Noltner, K. A., Buzin, C. H., Gu, D., Wen-Fong, C. Y., Nguyen, V. Q., Han, J. H., Lowstuter, K., Longmate, J., Sommer, S. S. Beyond Li Fraumeni Syndrome: Clinical characteristics of families with p53 germ line mutations. *J Clinic Oncol*. 2009;27:1250-1256.
38. Bougeard, G., Sesboue, R., Baert-Desurmont, S., Vasseur, S., Martin, C., Tinat, J., Brugieres, L., Chompret, A., dePaillerets, B. B., Stoppa-Lyonnet, D. Molecular basis of the Li-Fraumeni syndrome: An update from the French LFS families. *J Med Genet*. 2008;45: 535-538.
39. Brosh, R., Rotter, V. When mutants gain new powers: news from the mutant p53 field. *Natural Rev Cancer*. 2009;9:701-713.
40. Figueiredo, B. C., Sandrini, R., Zambetti, G. P., Pereira, R. M., Cheng, C., Liu, W., Lacerda, L., Pianovski, M. A., Michalkiewicz, E., Jenkins, J. Penetrance of adrenocortical tumours associated with the germ line TP53 R337H mutation. *J Med Genet*. 2006;43:91-96.
41. Roth, J. A. p53 prognostication: Paradigm or paradox? *Clinic Cancer Res*. 1999;5:33-45.
42. Russo, A., Bazan, V., Iacopetta, B., Kerr, D., Soussi, T., Gebbia, N. The TP53 colorectal cancer international collaborative study on the prognostic and predictive significance of p53 mutation: Influence of tumor site, type of mutation, and adjuvant treatment. *J Clinic Oncol*. 2005;23:7518-7528.
43. Bazan, V., Agnese, V., Corsale, S., Calo, V., Valerio, M. R., Latteri, M. A., Vieni, S., Grassi, N., Cicero, G., Dardanoni, G. Specific TP53 and/or Ki-ras mutations as independent predictors of clinical outcome in sporadic colorectal adenocarcinomas: Results of a 5-year Gruppo Oncologico dell'Italia Meridionale (GOIM) prospective study. *Annals Oncol*. 2005;16:50-55.
44. Iacopetta, B., Russo, A., Bazan, V., Dardanoni, G., Gebbia, N., Soussi, T., Kerr, D., Elsaleh, H., Soong, R., Kandioler D. Functional categories of TP53 mutation in colorectal cancer: Results of an International Collaborative Study. *Annals Oncol*. 2006;17:842-847.
45. Boeckler, F. M., Joerger, A. C., Jaggi, G., Rutherford, T. J., Veprintsev, D. B., & Fersht, A. R. (2008) Targeted rescue of a destabilized mutant of p53 by an in-silico screened drug. *Prot Nat AcadSci*, 105(30), 10360-10365.
46. Olivier, M., Langerod, A., Carrieri, P., Bergh, J., Klaar, S., Eyfjord, J., Theillet, C., Rodriguez, C., Lidereau, R., Bieche, I. The clinical value of somatic TP53 gene mutations in 1,794 patients with breast cancer. *ClinicCancer Res*. 2006;12:1157-1167.
47. Langerod, A., Zhao, H., Borgan, O., Nesland, J. M., Bukholm, I. R., Ikdahl, T., Karesen, R., Borresen-Dale, A. L., Jeffrey, S. S. TP53 mutation status and gene expression profiles are powerful prognostic markers of breast cancer. *Breast Cancer*

- 554 Res. 2007;9:1-30.
- 555 48. Ozcelik, H., Pinnaduwa, D., Bull, S. B., Andrulis, I. L. Type of TP53 mutation and
- 556 ERBB2 amplification affects survival in node-negative breast cancer. Breast Cancer
- 557 Res Treatm. 2007;105:255-265.
- 558 49. Soerjomataram, I., Louwman, M. W., Ribot, J. G., Roukema, J. A., Coebergh, J. W.
- 559 An overview of prognostic factors for long-term survivors of breast cancer. Breast
- 560 Cancer ResTreatm. 2008;107:309-330.
- 561 50. Harris, L., Fritsche, H., Mennel, R., Norton, L., Ravdin, P., Taube, S., Somerfield, M.
- 562 R., Hayes, D. F., Bast, R. C. American Society of Clinical Oncology 2007 update of
- 563 recommendations for the use of tumor markers in breast cancer. J Clinic Oncol.
- 564 2007;25:5287-5312.