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Tumour Biology: p53 Gene Mechanisms

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Abstract

Tumour is a sum of genetic errors with constantly proliferating cells. Development of cancer requires altered mechanism in just one cell resulting in unlimited replication of that cell. Inspite of several genetic insults that occur there are few cells which turn neoplastic. Thus, suggesting of a very powerful protective mechanism at work. p53, a tumour suppressor gene, is cancer prophylactic for most multicellular organisms and the single most unifying factor in the disease. For most kinds of cancer to develop, p53's suppressor activities have been disabled. There has been stupendous increase in knowledge on p53, but the pattern has grown much more complicated since then. The article provides an easy overview of p53 biology and different applications of p53 in tumorigenesis.

Introduction

Carcinogenesis is a multistep process. There are several families of genes that signal translation of protein molecules which transmit information between cells. The pathways of different signaling molecules interact with each other and so development is regulated by a complex signaling network. Most of the ongoing research is focused on tumour suppressors which influence the balance between cell cycle progression and cell death. This article describes p53 tumor suppressor gene signaling networks that have been implicated in cancer progression.

Mutations in tumor suppressor genes prevent unrestrained cellular growth and promote DNA repair and cell cycle checkpoint activation [1]. A suppressor gene can also be inactivated by a process called DNA methylation, which involves an enzyme called DNA methylase adding methyl groups to sites at or near the gene. This process is said to be 'epigenetic' because the sequence of bases in the DNA is not changed [2].

The first 'cancer gene' identified was derived from cancer-causing viruses and was known as 'oncogene'. Early experiments with somatic cell hybridization showed that tumor suppressor genes existed but were recessive, i.e. completely inactivated in malignancy [3].

In the literature, tumour suppressor genes have been variously named as `growth suppressor genes', `cancer suppressor genes', `oncosuppressor genes', `antioncogenes', `recessive oncogenes' and `gatekeeper genes' [4]. There is still no consensus on the general definition of a tumour suppressor gene [5]. In a broad sense, any gene that can protect cells from progressing towards neoplastic growth can be considered as a tumour suppressor gene [4].

Tumour-suppressor genes are the class of genes that regulate cell proliferation by acting as regulators of cell cycle [6,7]. Several tumour-suppressor genes have been identified like retinoblastoma (RB), p53, adenomatous polyposis coli (APC), wilms tumour (WT-1), deleted colon carcinoma (DCC) gene, mutated colorectal carcinoma (MCC) gene, patched (PTCH) gene and the neurofibromatosis type 1 (NF1) gene [8,9].

p53 Tumour Suppressor Gene

TP53 gene or gene product is a common cellular target in human carcinogenesis provoked by physical factors, chemical carcinogens or tumour viruses [7]. The p53 gene encompasses 16-20 kb of DNA on human chromosome 17pl3.1 [10]. The product of p53 gene is a 393-amino-acid nuclear phosphoprotein (about 53 kD in molecular weight) also known as protein 53 (p53) or tumour protein 53. It was first discovered in 1979 as a cellular protein which was bound to the viral oncoprotein in cells transformed by simian virus 40 (SV40). The p53 protein is a DNA binding protein found in very low quantities in normal cells; localized to the nucleus but larger quantities of p53 (5-100 folds) could be detected in transformed cells in culture and in tumour cells [11].

Regarded as the "guardian of the genome" and the "cellular gatekeeper", p53 exerts its tumour suppressor activity by downregulating genes governing proliferation and up regulating genes involved in preventing growth [12]. As a tumour suppressor, p53 is essential for preventing inappropriate cell proliferation and in maintaining genomic integrity following genotoxic stress. Following various intracellular and extracellular stimuli such as DNA damage (by means of ionizing radiation, UV radiation, application of cytotoxic drugs or chemotherapeutic agents and infectious viruses), heat shock, hypoxia and oncogene overexpression, wild-type p53 is activated and plays a pivotal role in triggering diverse biological responses, both at the level of a single cell as well as in the whole organism [13].

p53 Gene Activation Involves Three Basic Steps

Stabilization of p53

It is primarily achieved through events that disrupt its interaction with Mdm2, a negative regulator that mediates an ubiquitin mediated degradation of p53. For example, in response to DNA damage from ionizing radiation or certain chemotherapeutic agents, p53 is post-translationally modified including phosphorylation of the amino terminal region at specific amino acids by various kinases. The amino-terminal phosphorylation of p53 prevents Mdm2 binding, resulting in

the stabilization of p53. p53 stabilization also occurs in response to oncogenic challenges to the cell, although this response is primarily mediated through the antagonism of the p53–Mdm2 interaction by the tumour suppressor p14ARF (Alternate Reading Frame) [14].

Sequence specific DNA binding

Following its stabilization, p53 binds to DNA in a sequence-specific manner. The DNA-binding domain of the p53 protein is a "hot spot" for mutation, as the majority of tumour associated mutations in p53 occur within this region [15]. p53 also contains a carboxyl terminal basic DNA binding domain, originally shown to inhibit p53 binding to sequence-specific DNA in *invitro* assays. However, a recent finding of stress-induced, sequence-specific DNA binding suggests that a significant portion of p53 is bound to DNA in unstressed cells via the carboxyl terminal domain [16].

Transcriptional activation

p53 promotes transcriptional activation or repression of target genes by interacting with general transcriptional factors such as TFIID (Transcription Factor II D) [17]. Genes activated by wild-type p53 are functionally diverse and constitute downstream effectors of signaling pathways that elicit diverse responses such as cell-cycle checkpoints, cell survival, apoptosis and senescence. These genes include genes involved in cell cycle arrest, DNA repair, apoptosis and senescence-related genes such as genes p21/Cip1 (Cyclin dependent kinase interacting protein 1), Gadd45 (growth arrest and DNA-damage inducible protein 45) and genes of the Bcl-2 family [13].

p53 activation basically depends on cell type, environmental milieu and the nature of the stress. In response to sustained or severe stress signals, p53 leads to irreversible apoptosis or senescence. p53 triggered apoptosis involves the transcriptional induction of both the extrinsic and intrinsic death pathways including BAX, FAS, NOXA and PUMA [18,19].

Numerous p53 target proteins function to inhibit apoptosis including p21, decoy death receptors such as DcR1 and DcR2, the transcription factor SLUG (which represses the expression of PUMA) and several activators of the AKT/PKB (protein kinase B) survival pathways [20]. In some cases, p53 responds to potent stress by inducing cellular senescence through transcriptional activation of target genes such as p21, PAI1 and PML [21].

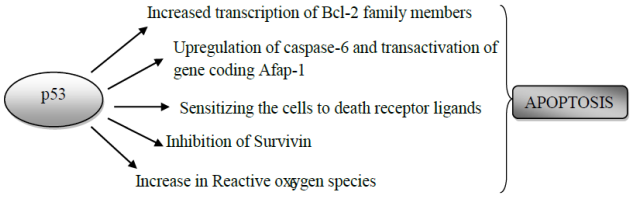

Figure 1: p53 and Apoptosis

Under conditions of lower levels of stress, when repair is possible, p53 causes cell-cycle arrest and DNA repair to allow cells to pause and repair any damage, thereby limiting the propagation of oncogenic mutations. Another protective, pro-survival mechanism is the capacity of p53 to up regulate the expression of antioxidant genes, such as sestrins 1 and 2 (SESN1 and SESN2, respectively), GPX1 and TIGAR which suppress the accumulation of reactive oxygen species, thereby maintaining genomic integrity [22,23] (Figure 1).

p53 can also limit tumorigenesis through autophagy or 'self- eating', which can provoke cell death through the activation of genes such as AMPK, DRAM, SESN1 and SESN2. p53 can also exert non-cell-autonomous effects that are pivotal to tumor suppression; the ability to impede angiogenesis through induction of gene products such as thrombospondin-1 (TSP-1) and inhibition of tumor growth and metastasis by stimulating signaling from the fibroblast compartment of tumors [24,25] (Figure 2).

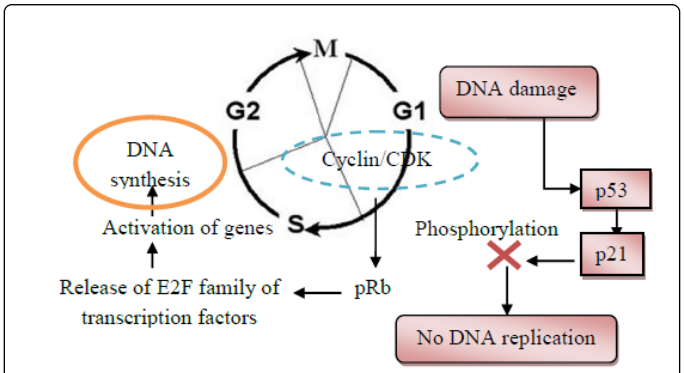

Figure 2: p53 and G1-S checkpoint.

The G1/S checkpoint prevents initiation of DNA replication in cells that have damaged DNA. Expression of p53 following DNA damage, arrests cells at the G1/S transition. Cell cycle progression is driven by phosphorylation events mediated by cyclin/CDK complexes. Cyclin D/CDK4, Cyclin E/CDK2 and Cyclin A/CDK2 complexes sequentially phosphorylate the tumour suppressor pRb and its family members resulting in release of the E2F family of transcription factors and transactivation of genes involved in DNA replication. These cyclin/CDK complexes are thus the main targets of the effectors of the G1/S checkpoint. Following DNA damage, p53 induces the expression of the CDK inhibitor p21. p21 once induced, localizes to the nucleus in wild-type p53 cells undergoing G1 arrest, but not in cells expressing mutant p53. Mouse embryo fibroblasts derived from p21 deficient mice have an impaired DNA damage induced G1 arrest [26].

The critical cyclin B1/CDC2 complex is the main target of the G2 checkpoint and involves the activation of the ATM (Ataxia telangiectasia mutated protein*)* and ATR (Ataxia telangiectasia and Rad3-related protein*)* and their downstream substrates Chk1 and Chk2 (Checkpoint kinase 1 and 2). p53 is involved in the maintenance rather than the initiation of the G2 arrest. Several p53 target genes are shown to play a role in the p53 induced G2 arrest. Cdc25C, the phosphatase that promotes mitosis is inhibited after DNA damage through phosphorylation at Ser216 by Chk1, Chk2 and other kinases. This modification creates a binding site for 14-3-3δ regulatory protein and this association sequesters Cdc25C in the cytoplasm and/or inhibits its phosphatase activity. Cdc25C has been shown to be a target of repression by p53 following DNA damage [27] (Figure 3).

In addition, a particular 14-3-3δ isoform, 14-3-3s, is also a p53 target gene and is upregulated following DNA damage. 14-3-3s prevents proper nuclear localization of cyclin B1/CDC2 after DNA damage. Although it has been suggested that p21 is a poor inhibitor of CDC2 *invitro* compared to other cyclin dependent kinases, p21 has

also been implicated in the sustained G2 arrest, through inhibition of the cyclin B1/CDC2 complex activity [28].

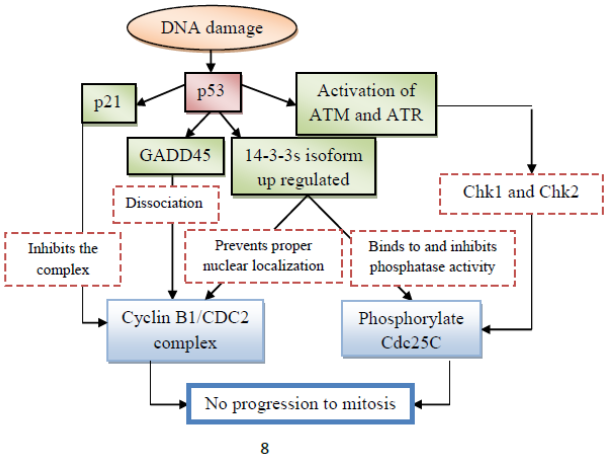

Figure 3: p53 and G2-S checkpoint.

Another p53 target gene involved in the G2 arrest is GADD45. GADD45 also interacts with CDC2 and inhibits its kinase activity, presumably by causing dissociation of the cyclin B1/CDC2 complex. Further, induction of GADD45 results in G2 arrest associated with increased cytoplasmic cyclin B1. Of note, induction of G2 arrest by GADD45 requires the presence of wild-type p53 and depends on the type of DNA damage [26]. The functions of p53 are summarized in Table 1.

Sl. No.	Functions	Mechanisms
1.	Prevents the transmission of damaged genetic information from one cell generation to the next.	Binding to a transcription factor called E2F. This prevents E2F from binding to the promoters of protooncogenes such as c-myc and c-fos. Transcription of c-myc and c-fos is needed for mitosis to block the transcription factor needed to turn on the genes preventing cell division.
2.	Initiates apoptosis if the damage to the cell is severe	Works as an emergency brake on cancer development by killing cells that attempt to proliferate in oxygendeficient regions of tumors.
3.	Transcription factor	Represses transcription of one set of genes (several of which areinvolved instimulating cell growth) while stimulating expression of other genes involved in cell cycle control.By stimulating the transcription of the p21 gene (negative regulator of cyclindependant kinases), p53 prevents cell proliferation.

Table 1: Functions of p53 [29].

Sequence-specific DNA binding of p53 is a prerequisite for the transactivation of target genes. Typically, p53 response elements (p53REs) are located within a few thousand nucleotides upstream or downstream from the transcription start site. Frequently, p53 targets contain at least two widely spaced p53REs. However, not all target genes are equally responsive to p53, suggesting additional layers of regulation. The interaction between p53 and its DNA target sequences is highly influenced by the cellular context [30].

A plethora of partner proteins have been implicated in modulating the selection of p53 targets. Some of those proteins are transcription factors themselves, which presumably bind to promoter sites adjacent to p53REs to selectively induce specific response genes. Others influence the ability of p53 itself to bind preferentially to particular DNA target sequences and not to others. The cellular environment as well as the relative abundance of these potential partners under different conditions could obviously tip the life-or-death balance of p53 activity [30] (Figure 4).

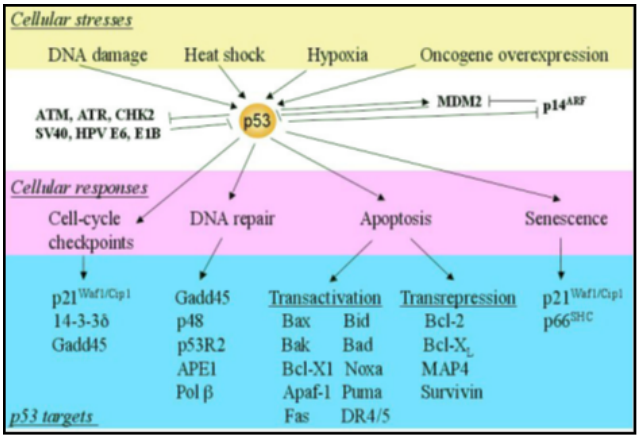

Figure 4: Summary of p53 functions.

Additional transcriptional programs controlled by p53 in regulating metabolic pathways are being unraveled. For example, modulating glucose uptake [31], enhancing mitochondrial respiration [32], inhibition of glycolysis (through TIGAR) and promoting oxidative phosphorylation (through SCO2) to protect cells from metabolic reprogramming-known as the 'Warburg effect'-which is considered significant in malignant transformation [33].

Posttranslational Modifications of p53

In response to stress, p53 activity and its stabilization are also highly governed through complex networks of posttranslational modifications including phosphorylation, acetylation, ADP-ribosylation and ubiquitylation. Most of these modifications occur in the N- and C-terminal regions of p53. Posttranslational phosphorylation and acetylation are the main modifications enhancing the transcription activating ability of p53 because these modifications generally result in p53 stabilization and accumulation in the nucleus, where p53 interacts with sequence-specific sites of its target genes. Posttranslational modifications also prevent p53 from being targeted for degradation as these modifications of p53 at distinct sites may abolish the interaction between MDM2 and p53 [34].

Phosphorylation

Phosphorylation has been regarded as the most commonly reported protein modification that occurs in mammalian cells. Phosphorylation

of p53 generally results in its stabilization and has also been shown to increase its sequence-specific DNA binding. Twenty serine and threonine sites on p53 have been identified to be phosphorylated in human cells following DNA damage induced by ionizing radiation or UV irradiation. Most of these sites are located in the N-terminal region, but there are also sites in the C-terminal domain and in the central core [35].

Many protein kinases have been implicated in the phosphorylation of p53. Different protein kinases phosphorylate several sites on p53 and in some instances the same site can be phosphorylated by more than one protein kinase. For example, phosphorylation at Ser15 is mediated by ATM/ATR, either directly or through Chk1/Chk2 or at Ser20 by Chk1/Chk2. Stress-induced N-terminal phosphorylation increases p53 stability by dissociating the negative regulator MDM2 [36].

Acetylation

Acetylation has a crucial role in stabilization of p53 and p53 transcriptional activation. Acetylation involves lysine residues on p53 and all are located in the C-terminal region. These acetylated residues are located in the regulatory domains adjacent to the tetramerization domain. Two histone acetyltransferases (HATs) are known to acetylate p53 i.e. p300 and PCAF (p300/CBP-associated factor) acetylates. The acetylation of p53 can dramatically stimulate its sequence-specific DNA binding activity, possibly as a result of an acetylation-induced conformational change. It has been shown that acetylation by p300 and PCAF enhances the transactivation activity of p53 in cells, whereas deacetylation of p53 suppresses such activity [37].

Acetylation may also regulate the stability of p53 by inhibiting its ubiquitylation induced by Mdm2. The ubiquitylation and acetylation of p53 occur at the same sites in the C-terminus suggesting that these modifications may compete for the same residues. The acetylation sites on p53 are essential for ubiquitylation and subsequent degradation of p53 by Mdm2. Thus, p53 acetylation is directly involved in the regulation of its ubiquitylation and subsequent proteolysis induced by Mdm2. Inhibition of p53 deacetylation leads to a longer half-life of endogenous p53 suggesting that acetylation of p53 may also contribute to p53 stabilization [34].

Ubiquitination

Ubiquitination is the addition of ubiquitin molecules to lysine residues of a protein. Following ubiquitination, most proteins are targeted to proteosome for degradation. This is the mechanism used for the rapid turnover of p53 protein. Ubiquitination involves numerous proteins, but the specificity depends on the specific E3 ubiquitin ligase enzyme which attaches an ubiquitin molecule to the correct substrate. The Mouse double minute 2 (Mdm2) proteins is the ligase used to ubiquitinate p53, which covalently attaches ubiquitin groups to p53 and causes the degradation of p53 through ubiquitin mediated proteolytic pathway [38].

Regulation of p53 Protein Localization

p53 function depends on nuclear localization and both nuclear import and nuclear export of p53 are tightly regulated. Nuclear import of p53 is dependent on its interaction with the microtubule network and dynein, a molecular motor protein indicating that p53 is actively transported towards the nucleus where nuclear localization signals within the C-terminus of p53 allow efficient nuclear import. p53 also contains a nuclear export signal within its C-terminus, although efficient export of p53 to the cytoplasm depends on Mdm2 function. Recent studies have shown that the ubiquitin ligase activity of Mdm2 is critical for the nuclear export of p53 [69]. Ubiquitination of p53 by Mdm2 occurs within the C-terminus of the p53 protein and mutation of these lysine residues inhibits Mdm2 directed nuclear export of the p53 protein. Some studies suggest that efficient degradation of p53 requires nuclear export, so Mdm2's E3 ligase activity may play a dual role in regulating the stability of p53, both in allowing nuclear export and in targeting p53 to the proteasome [39] (Figure 5).

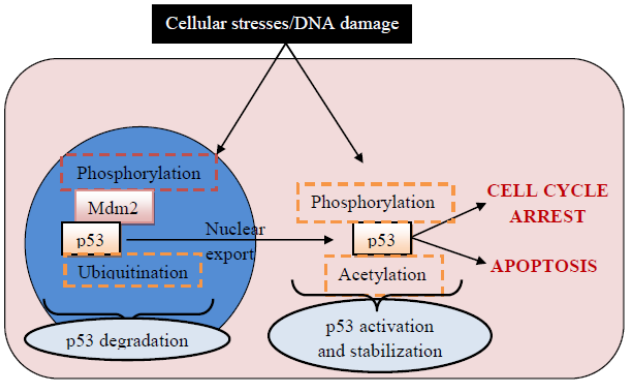

Figure 5: Regulation of p53.

Improper p53 activity can be destructive to cell and organism viability, and there are therefore numerous mechanisms to keep p53 in check. Several E3 ubiquitin ligases – MDM2, PIRH2, COP1 and ARF-BP1-negatively regulate p53 protein levels, keeping levels low when p53 activity is not required [40]. In a negative feedback loop, Mdm2 is itself induced by the p53 protein. However, when cells or cellular DNA are damaged, the cells increase p53 expression. The accumulation of wild-type p53 switches off the cell cycle until the damage is repaired. If the repair fails, p53 may further trigger controlled cell death through apoptosis. However, mutant p53 proteins often do not induce Mdm2 and are thus able to accumulate at very high concentrations [41].

In the absence of functional Mdm2 protein, p53 becomes strongly deregulated. In certain human cancers; excessive Mdm2 expression, achieved through mdm2 gene amplification or other mechanisms, can lead to constitutive inhibition of p53 and thereby promote cancer without a need to alter the p53 gene itself. Excess Mdm2 can also promote cancer independently of p53 [29]. The evidence is provided that the human proto-oncogene BCL6 has a repressive effect over p53 gene transcription, by binding two specific DNA motifs within its promoter. BCL6 is abundant in germinal-center B cells where there is no p53 gene expression [42]. In contrast, there is a positive feedback loop where the p73 or p53 protein directly binds to the p53 gene promoter and transactivates its expression both in physiological conditions and in response to cellular stress [43]. These brings to light the importance of p53's auto regulation and that when disrupted it can lead to defects in cell cycle regulation and suppression of p53-mediated apoptosis [44].

Schroeder et al provided the first experimental evidence for DNA methylation dependent silencing of the p53 gene promoter using a reporter gene construct [45]. By means of *invitro* DNA methylation, 90% reduction in gene expression was obtained. Some studies have

documented from patient samples in primary hepatocellular carcinoma, acute and chronic lymphoblastic leukemia [46,47]. The aberrant regulation of p53 gene promoter by DNA methylation remains controversial due to several inconsistencies in the literature and an apparent lack of direct methylation over the p53 core promoter [48].

p53 in Tumorigenesis

The molecular mechanisms by which the p53 is involved in tumorigenesis are not fully understood. A substantial amount of evidence has been provided over the past few years implicating p53 in the development of wide range of malignancies [7]. p53 gene is mutated in about 50% of human cancers of breast, colon, lung, liver, prostate, bladder and skin. Mutations occur due to carcinogens that affect p53 such as ultraviolet radiation and cigarette smoke. These mutations are missense in 80% of cases, nonsense in 7.5%, deletions, insertions or splicing mutations (12.5%).

Infection with viruses introduces foreign DNA into the cells. For example, upon infection with Simian Virus 40 (SV40), viral proteins are produced within the cell cytoplasm such as large T antigen which binds and inactivate p53 protein. Other viruses such as Hepatitis and Human papillomavirus produce similar proteins. The elimination of functionalp53 from the cells clears the way for cell division even in the presence of DNA damage. The mutant p53 protein does not bind to DNA in the same manner as wildtype p53.In the absence of p53, genetic instability as evidenced by increased mutations and aneuploidies are likely to increase.

The increase in genetic damage leads to the accumulation of defective tumor suppressors and oncogenes. Mutant p53 proteins acquire oncogenic properties that enable them to promote invasion, metastasis, proliferation and cell survival [29]. Most cancer-associated p53 mutations destroy all tested activities of p53, a few tumours harbour mutations in p53 that allow the protein to retain its cell cycle arrest function but selectively lose its ability to induce apoptosis [20]. Oncogenic changes that promote cancer cell proliferation and survival are often accompanied by alterations in pro-survival functions of p53, which might protect cells undergoing repair following mild stress but would be extremely counterproductive if maintained in irreparably damaged cells [49]. Although metabolic activities are integrated into the tumour suppressive functions of p53, deregulation of some elements of the p53-induced response might also provide tumours with a survival advantage [50]. Since the loss of p53 function is so prevalent in human cancer, this protein is an ideal candidate for cancer therapy [29]. Table 2 summarizes p53 malfunctioning in various tumours.

Growing Complexity of p53

As p53 activity is impaired or defective in most human cancers, the aim is to re-establish the growth-inhibitory functions of p53 in cancer cells. This approach has been supported by animal studies where reactivation of wild-type p53 leads to efficient tumour. One more therapy is reactivation of p53 by the use of gene therapy to reintroduce p53 into tumour cells by means of vectors such as adenoviruses. Small molecule drugs have been developed that stabilize and activate the p53 protein. Although these drugs function by interfering with the ability of Mdm2 to tar-get p53 for degradation, cell-based drug screens have also identified inhibitors of sirtuins-protein deacetylases that can restrain p53 activity-as effective p53-activating agents [20].

Mechanism of inactivation of p53	Tumours	Effect of inactivation
Amino acid mutation in the DNA binding domain	Colon, breast, lung, bladder, brain, pancreas, stomach and esophagus	Prevents p53 from binding to specific DNA sequences and activating the adjacent genes
Deletion of carboxyl terminal domain	Occasional tumours at many other sites	Prevents the formation of tetramers of p53
Multiplication of Mdm2 gene in the genome	Sarcomas and Brain tumours	Extra Mdm2 stimulates the degradation of p53
Viral infection	Cervix, Liver and Lymphomas	Products of viral oncogenes bind to and inactivate p53 in cell, in some cases stimulate p53 degradation
Deletion of p14 gene	Breast, brain, lung and others (especially when p53 is not mutated)	Failure to inhibit Mdm2 and maintains p53 degradation under control
Mislocalization of p53 to the cytoplasm, outside the nucleus	Neuroblastomas, Breast carcinoma	Lack of p53 function (p53 functions only in the nucleus)

Table 2: Many ways in which p53 malfunctions in human cancers [51].

Conclusion

p53 is a crucial tumour suppressor gene that responds to diverse stress signals and functions as guardian of our cells by stopping the cell cycle, instructing a cell to commit suicide and preventing cells with DNA damage from dividing and passing on harmful mutation to daughter cells leading to tumour suppression. p53 remains a highly dynamic and rapidly expanding area of study. Efforts to identify new gene therapies and to determine how they work will help researchers and clinicians design better ways to detect, treat and prevent cancer. Meanwhile, advances in our understanding of p53 will continue to provide insights critical to the development of novel anti-cancer approaches.

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