p53: The molecular guardian of cell cycle

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p53 is a tumour suppressor gene acting as a checkpoint to regulate the cell cycle under adverse conditions. This function is performed by increasing the transcription of some genes and repressing the transcription of others leading to either G_1 arrest of damaged cells or apoptosis, if DNA damage is irrepairable. In most of human cancers p53 is either mutated or inactivated by oncoproteins of several tumour viruses and various cellular proteins, leading to malignant transformation. Thus, p53 acts as a molecular guardian of genomic stability by keeping in check the tumourigenesis associated with DNA-damaging agents.

OVER the past few years, remarkable progress has been made in identifying the molecules that drive the cell cycle. These have been broadly classified into three groups: (a) those that are obligatory for the progress of cell cycle, e.g. cdc (cell division cycle) like kinase and cyclins[1], (b) those which monitor the efficacy and completion of obligatory events, thus acting as checkpoints[2,3]; (c) those that mediate the communication between the above two via signal transduction pathway. The genes involved in the signal transduction pathway are proto-oncogenes while those that act as cell cycle checkpoints are tumour suppressor genes. These tumour suppressor genes are not essential for the survival or growth of cell, but are responsible for increased fidelity of the cell cycle[2,3] and any alteration in their structure or failure on their part results in uncontrolled cell proliferation.

Many tumour suppressor genes have been identified so far (e.g. retinoblastoma susceptibility gene (Rb), Wilm's tumour gene (WT1), the deleted in colon carcinoma gene (DCC), the mutated in colorectal carcinoma gene (MCC), the adenomatous polyposis coli gene (APC), the neurofibromatosis type I gene (NF 1) and the p53 gene)[4,5]. Out of these only p53 has been shown to have characteristics of all the three groups described above. It is the most common gene mutated in human tumours. Its growth-suppressive effect is mediated through transcriptional activity of the protein, and overexpression of this protein results in arrest in G_1 phase of the cell cycle or induction of apoptosis[6,7].

In this review we will discuss briefly the structure of p53 protein along with the most important findings made during the past 12 months on its role in cell cycle and apoptosis. Special emphasis has been laid on the mechanism of its inactivation in tumours.

Structure of p53 protein

p53 protein is a 53 kDa phosphoprotein encoded by a gene of 20 kb localized on the short arm of chromosome 17 (17p13), consisting of 11 exons[8–13]. Its structure is conserved over the evolutionary scale (bearing 80% homology between human and murine protein and 56% homology between human and xenopus)[9]. Some regions of the protein are highly conserved and have been divided into five widely spaced amino acid clusters termed domains I–V (Figure 1). In some of these domains, the sequence conservation among all the species is perfect over stretches of 14 or more amino acids, indicating a high degree of functional importance. These five regions, I, II, III, IV and V, correspond to codons 13–19, 120–143, 172–182, 238–259 and 271–290 respectively (out of the total 393 amino acids). Of the p53 mutations 86% are located between codons 120 and 290 (extreme mutation hot-spots being 175, 248, 273 and 282) with 60% of these being missense mutations residing in conserved regions II, III, IV and V[14–16]. Both the distribution of mutations and the conservation of amino acid sequences in this region of the protein suggest that an important functional domain resides in this region of the protein.

The amino acid residues of the p53 protein have been divided into three distinct functional domains as well. The amino-terminal 75 amino acids are quite acidic, thus resembling fos, Gal4, glucocorticoid hormone receptor and proline-rich like other mammalian transcription factors such as fos, jun, oct-2 and SRF[17–20]. This region

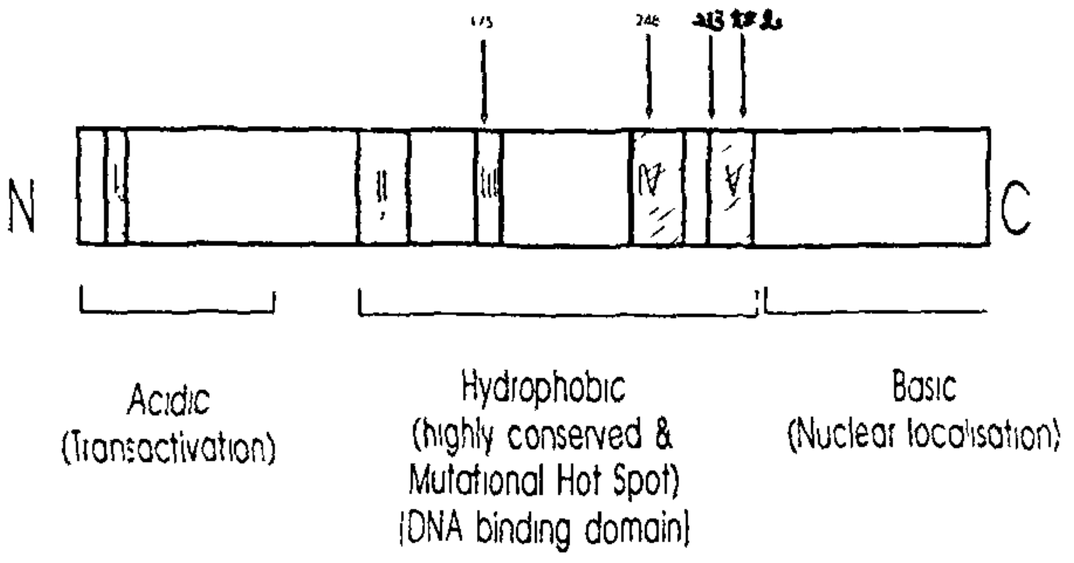

Figure 1. Structure of human p53 protein showing five highly conserved domains I–V corresponding to amino acids 13–19, 120–143, 172–182, 238–259 and 271–290. Extreme mutation hot-spots 175, 248, 273 and 282 are represented by arrows The functional domains of the protein involved in DNA binding, nuclear localization and transactivation have also been indicated.

has been shown to have transactivating function (20%). The region between residues 120 and 290 can act as a specific DNA-binding domain, interacting with a p53 recognition element. The consensus sequence of this p53 binding element is 5′-Pu-Pu-Pu-C-A-/T-A/T-G-Py-Py-Py-3′[21, 22]. The carboxy terminal domain composed of amino acid sequence 290–393 is highly basic and contains a set of nuclear localization signal[23], a site for phosphorylation by a cyclin-dependent kinase[24] and a region that promotes the protein to form tetramers and other oligomeric forms in solution[25].

Phosphorylation and dephosphorylation is an important regulatory mechanism of p53 activity and it is phosphorylated at multiple serine residues. Phosphorylation by $p34^{cdc-2}$ kinase at serine 315 helps in entry of p53 into the nucleus during cell cycle[26]. Casein kinase II also phosphorylates the serine at C-terminal, which is involved in attachment to 5.8s rRNA[27], although significance of this attachment is unclear. Phosphorylation of amino-terminal serine residues occurs by DNA-activated protein kinase[28].

Wild-type p53 as tumour suppressor gene

p53 was earlier thought to be an oncogene, as transfection of the p53 gene into rodent embryo fibroblasts led to transformation of the cells[29, 30] and it also cooperated with ras in transforming the rodent cells[31]. However, interpretations had to be altered when it was discovered that the wild-type p53 acts as a negative growth regulator and earlier results were misleading as mutant forms of p53 were used[32]. The ability of p53-deficient mice to develop normally showed that it is not required for cell division but the observation that these mice are susceptible to tumours suggests that it plays a global protective role in cells against tumour formation[33].

The first evidence of the potential role of normal p53 as a tumour suppressor was obtained from mouse fibroblast lines. On treatment with UV light or UV-mimetic drugs, p53 protein levels increased rapidly and this increase was due to increased stability of the protein due to post-translation modification[34]. Later on, a similar increase was observed in other cell lines with DNA-damaging agents (γ-irradiations and actinomycin D)[35, 36]. The increase in p53 levels in cells caused a temporary arrest in cell cycle at G1 phase. This arrest occurred in cells containing wild-type p53 and not with mutant p53[35]. The transfection of wild-type p53 into malignant cells lacking functional p53 restored G_1 arrest following ionizing radiations, thereby showing that p53 acts as a molecular gaurdian for genomic integrity[37, 38]. If DNA is damaged, p53 gets induced, stabilized or activated and arrests the cells until the damage is repaired; if not, then it initiates apoptosis[39, 40].

In pre-neoplastic and neoplastic cells lacking functional/wild-type p53, this monitoring mechanism is inactive and cells are genetically unstable due to the inability of the cells to repair fully the DNA before entering into S phase. Mutations, gene amplification and chromosomal aberrations accumulate due to the absence of p53 monitoring mechanism, leading to oncogene and tumour suppressor gene alterations and malignant progression[41].

Thus, p53 acts as a checkpoint control in cell cycle, blocking the progression of cells in G_1 phase and preventing entry into S phase in response to environmental insult. This does not permit duplication of damaged DNA and minimizes errors in the cell cycle, thus enhancing the fidelity of the cell cycle by monitoring cells for damaged DNA.

p53 protein accomplishes this function in one of the several ways. The enhanced levels of p53 protein regulate the transcription of a set of genes with p53 response element. Some of the genes implicated are:

GADD 45 (growth arrest and DNA damage inducible gene)

GADD 45 is induced in normal cells in response to DNA damaging agents[42]. p53 itself is an upstream regulator of GADD 45 in the radiation-induced signal transduction pathway, which controls cell cycle arrest following DNA damage[37]. γ-radiation-induced damage to DNA (primarily, strand breaks) is a major signal for activation of this p53-dependent pathway[43]. Its induction is rapid and transient and after DNA repair its levels decrease rapidly, as prolonged expression of GADD 45 is deleterious due to its inhibitory effect on growth.

mdm-2 (murine-double-minute-2)

This also has a p53 response element in the first intron of the gene. Its transcription is regulated by p53 as well as by mdm-2 itself[44]. mdm-2 has been classified as an oncogene as its product promotes the entry of cells into S phase. Increased levels of mdm-2 protein bind to p53 and reduce p53-mediated transcriptional activation[45].

WAF1/CIP1/Sdi1 (wild-type p53-activated fragment/cyclin-dependent kinase inhibitor protein/senescence-derived inhibitor protein)

Recently, p53 has been found to induce a tumour suppressor gene known as WAF1 or p21[46, 47]. When exposed to DNA damage, cells which contain endogenous wild-type p53 are stimulated to produce higher levels of protein. This induced p53 transcriptionally activates WAF1 expression by directly interacting with its

regulatory element. Induction of this 21 kDa protein and its transport to the nucleus results in association with and inhibition of cdk complexes[48]. Inhibition of these kinases prevents the phosphorylation of pRb; as a result, E2F (E2F is a transcription factor which induces the genes required for transition of cells from G_1 to S phase) is not released and the cells fail to exit G_1 (Figure 2).

The levels of WAF1 are quite high in quiescent cells, thereby preventing them from reentering cell cycle, while this property is lost in tumour cells, as a result of which they enter next cell cycle[48]. WAF1 is also induced through p53-independent pathway in the early G_1 phase, where it is thought to act as internal control mechanism to prevent cells from entering S phase prematurely by regulating the levels of cyclin-cdks[46]. Other cdks inhibitors are p16 and p27 (Figure 2) and, out of these two, p16 is involved in negative feedback regulation of cdks[49,50].

Thus, p53 exerts a multiple control for G_1 arrest. It may utilize the regulation of GADD 45 and WAFI to block progression through cell cycle in G_1 and mdm-2 to reverse this process and commit cells to S phase after the DNA repair process. At high doses of UV, cells induce p53 to high levels and the induction of mdm-2 mRNA and protein is delayed, occurring at about the same time as the cells enter S phase[1]. Thus, p53 could control the transcription of a set of genes to block cells in G_1 and then overcome this block to permit reentry into the cycle. However, it remains to be determined at what phase of cell cycle additional factors are required for p53-stimulated transcription of these genes.

So far, these are the only genes known to be induced by p53. p53 also suppresses the activity of genes involved in S phase such as histone H3 and PCNA (a component of DNA replication machinery) and the genes of the late G_1 stage, e.g. B-*myb* and DNA polymerase alpha gene. In addition to this, it also down-regulates the c-*fos*, β-actin, IL-6, c-*hsc* 70, Rb, MDR, *bcl-2* and certain viral genes[51–53]. The suppression of some of these genes occurs by binding of p53 to a basal transcription factor the TATA binding protein (TBP) and CCAAT binding factor (CBF), thereby blocking the transcription[54,55]. Mutated protein is unable to bind to these factors, as a result cells enter into S phase.

p53 also plays a direct role (not only via regulation of transcription of other genes) in the process of monitoring DNA or recombination intermediates in the cells. It binds with high affinity to single-stranded DNA and RNA and catalyses the annealing of these nucleic acids into double-stranded DNA or RNA[56]. It is speculated that p53 antagonises the helicase activity required for DNA replication and recombination. This blocks the aggressive single-strand recombination intermediates that lead to gene duplications, amplifications and oncogene activation. It interacts with replication protein A (RPA) (involved in DNA replication and excision repair by binding to single-stranded DNA) and interferes negatively with its capacity to bind single-stranded DNA, thus inhibiting the entry of cells into S phase[41,57]. p53 inhibits the guanine nucleotide biosynthesis as well, but it is not clear whether this effect is direct or indirect[58].

Thus, p53 acts as a general transcription factor regulating the expression of many genes. But how the regulation of p53 occurs has not been well worked out as yet. Deffie *et al.*[59] have shown that p53 contains a p53 response element and it can regulate its own transcription, although the direct interaction of p53 protein to its promoter has not been observed. In addition to this, promoter region of p53 also contains a consensus sequence for binding of basic helix loop helix (bHLH) containing transcription factors such as myc, USF and TFE3. So far, only USF has been shown to enhance the activity of p53 promoter by binding to this sequence[60].

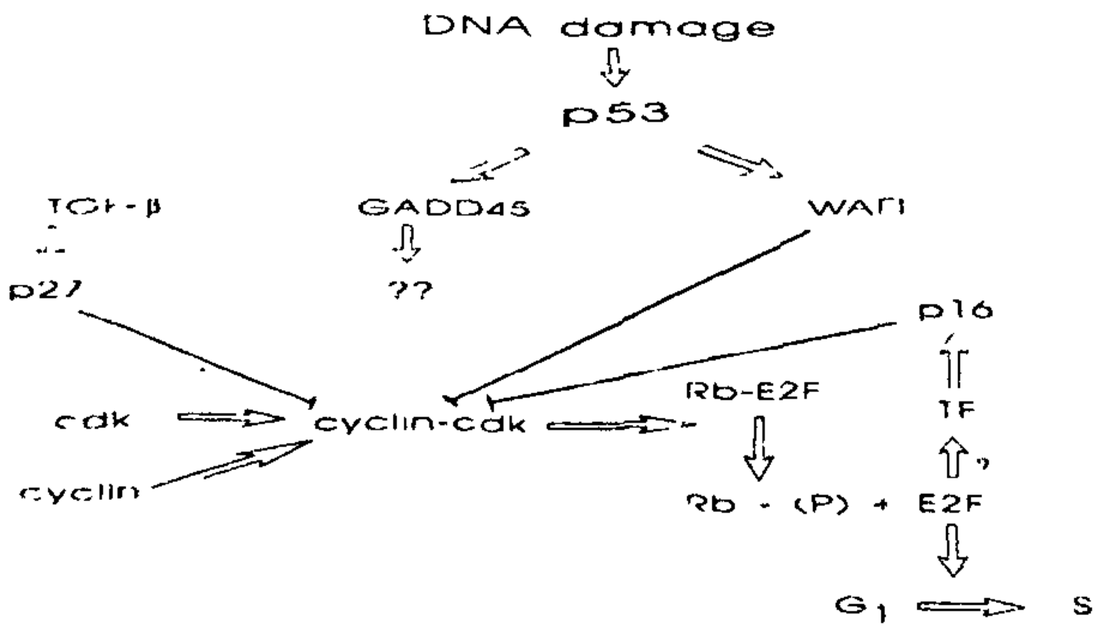

Figure 2. Role of p53 in control of cell cycle. The catalytic subunit of cdk binds to its regulatory subunit cyclin to form active cyclin-dependent kinase, which phosphorylates retinoblastoma protein. This results in release of E2F, a transcription factor for many genes required for entry into S phase. The feed back regulation of cdks occurs by another tumour suppressor gene p16. In case of DNA damage p53 levels increase, which, in turn induce WAF1, which forms a complex with cdks and inhibits their activity, thereby leading cell cycle arrest at G_1.

p53 in apoptosis

As mentioned earlier, following irradiation-induced damage[41,57], p53 switches off replication until damage is repaired, but if the repair fails, p53 triggers apoptosis. This induction of apoptosis occurs via p53-mediated down-regulation of bcl-2 expression in the cells (bcl-2 is an inhibitor of apoptosis) and a simultaneous increase in expression of bax (dominant inhibitor of bcl-2)[51,61,62] (Figure 3). The expression of bcl-2 is inversely correlated with the expression of fas antigen, which is directly involved in deletion of unfavourable clones[63].

Recently, it has been shown that another protein WAF1 is involved in p53-mediated apoptosis[46,47]. How-

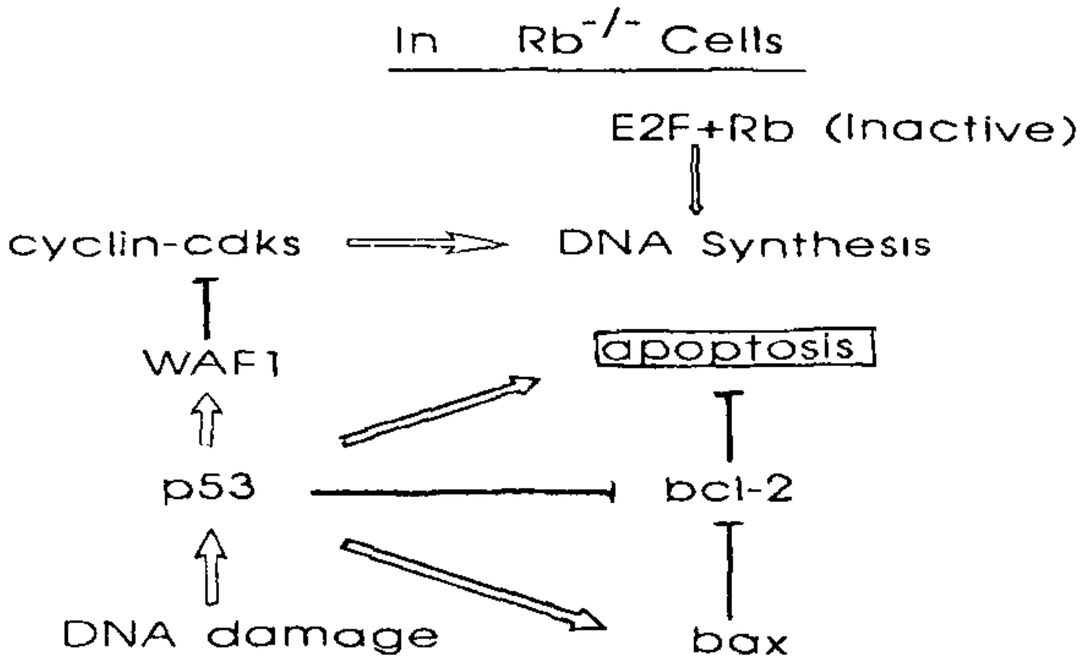

Figure 3. Role of p53 in apoptosis In cells which are $Rb^{-/-}$, E2F is not bound to pRb and is in active stage. So, the cells get a signal to enter into S phase. Growth arrest induced by p53 conflicts with the DNA synthesis induced by E2F and in this case p53 induces apoptosis by down-regulation of bcl-2 (arrows represent induction and lines show inhibition)

ever, it remains to be determined whether WAF1 interacts with bcl-2 to cause apoptosis or not.

p53 also acts as a safeguard mechanism and compensates for the inactivation of retinoblastoma gene (another tumour suppressor gene). In normal cells, proliferation is inhibited through activation of two pathways: (a) cyclin-dependent kinase inhibitor, e.g. WAF1 induced by p53 and (b) functional sequesteration of E2F by Rb. In the absence Rb, E2F activation stimulates DNA synthesis, whereas wild-type p53 tends to arrest the cells at G_1 via WAF1. A conflict of signals occurs between growth-promoting action of activated E2F and growth suppressive action of p53; as a result, p53 induces apoptosis[64–66] (Figure 3). In the absence of p53 safeguard mechanism in $Rb^{-/-}$ cells, uncontrolled cell proliferation occurs through E2F activation, leading to cancerous state.

Functional inactivation of p53

As p53 acts as a guardian of genomic stability, any alteration in the structure of p53 will lead to decreased stability of genome, resulting in development of a wide range of malignancies. However, studies have shown that p53 mutations are rare in early stages of cancer[67]. The initiation of cancer in the cells may occur due to alteration, overexpression or inactivation of a gene product involved in cell cycle progression and regulation, e.g. overexpression of myc leads to cancerous growth and alteration in structure of ras results in continuous signalling; as a result, cells continue to proliferate. Later on, p53 becomes more susceptible to mutations in these cases, and point mutations occur in one allele, followed by loss of function in second allele. These mutations cause the transformation of benign tumour to malignant state[67, 68]. This shows that functional inactivation of p53 is a key genetic event for progression of various malignancies. the mechanisms by which functional inactivation of p53 occurs are as follows.

Mutations

About 60% of all human cancers have mutations in p53 gene[69] and about 85.6% of the mutations at p53 locus in human cancers are missense mutations resulting in a faulty or altered protein in the cell[15]. This is in contrast with other tumour suppressor genes (Rb, APC), which have much higher frequencies of chain termination codons, deletions, exon skipping mutations or frameshift mutations. Only 8.1% of p53 mutations are deletions or insertions, 5.5% are nonsense or frameshift mutations and 0.8% are neutral[69]. The most common type of mutations are transitions and transversions at C : G or CpG dinucleotides[15] (Table 1).

These somatic mutations are found in both alleles, or, more commonly, a mutation in one allele is followed by a loss or reduction to homozygosity of second allele (the loss of heterozygosity is caused by mitotic recombination, gene conversion and nondisjunction rather than by independent second mutation)[70]. The tissues with wild-type p53 are resistant to tumour formation. If cells are heterozygous for p53 allele ($p53^{+/-}$), they develop soft-tissue sarcomas and osteosarcomas and in homozygous condition ($p53^{-/-}$) malignant lymphomas are formed. Germline p53 mutations are also found in some families, e.g. patients with Li Fraumeni syndrome have one mutant and one wild-type p53 allele and these patients are predisposed to various cancers[71, 72].

The mutant p53 protein exhibits several phenotypes

Table 1. Nature of p53 gene point mutations in different types of cancers

	Mutations at G : C		
Cancer location	At G · C base pair	At CpG dinucleotide	Mutations at A : T
Colon cancer	15	67	18
Breast cancer	70	13	17
Lymphomas and leukemias	18	47	36
Liver cancer	95	01	5
Lung cancer (SCLC)	45	31	13
(Non-SCLC)	80	10	10
Sarcomas	47	53	0
Brain tumours	40	45	15

Values given are in percentage mutations
SCLC: Small-cell lung cancer.

or activities which suggest that they actively contribute in some fashion to abnormal cell growth. The mutated protein can cooperate with an activated *ras* oncogene and transform the cells[31]. The mutated protein loses tumour suppressor function, but gains some new activities such as

- binding to hsc 70, which helps in translocation of the mutated protein to nucleus[73],
- stimulating the growth by activation of certain genes[52,61],
- substituting the function of bcl-2 by overcoming apoptosis[61],
- activating multidrug resistance gene (MDR1), thus making the tumour cells resistant to chemically unrelated drugs[52].

Inactivation by interaction with viral oncoproteins

It has been well demonstrated that inactivation of wild-type p53 occurs due to binding to transforming proteins of DNA tumour viruses[14]. Binding of p53 to SV40 large T antigen[74,75] or adenovirus E1B[76] protein leads to an increased half-life of p53 and inactivates its normal function by formation of stable complexes. As p53 is a negative growth regulator which can arrest cells in late G_1[51], removal of a significant fraction of p53 by complexing to T antigen could tip the cell into S phase. Consequently, loss of normal p53 activity by binding to T antigen provides a cellular environment (S phase) more amenable to the replication of SV 40 DNA.

Adenovirus E1B protein binds to p53 and the binding region is situated in the amino-terminal acidic domain, which is associated with transcription–transactivating function of p53, thereby increasing the transforming potential[77–79].

E6 proteins of oncogenic human papilloma viruses HPV-16 and HPV-18 bind to p53 and stimulate the degradation of bound p53 through ubiquitin-dependent proteolysis[80].

p53 inactivation by cellular proteins

The inactivation of p53 occurs by binding to a cellular protein of 90 kDa (mdm-2) which was copurified along with p53 following immunoprecipitation with p53-specific monoclonal antibody[81]. Binding of mdm-2 to acidic domain of p53 reduces its transactivation ability[82].

mdm-2 is frequently amplified in human sarcomas[83]. In some of these tumours no p53 mutations were observed, suggesting that overexpression of mdm-2 effectively abrogated wild-type p53 activity[84]. However, it has been demonstrated in the murine tumours induced by carcinogenic agents that all the tissues did not have mdm-2 amplification or p53 alteration, indicating the existence of alternative pathway that permits tumour cells to bypass p53–mdm-2 control[85,86].

Functional inactivation by change in conformation

In addition to its ability to interact with heterologous proteins, p53 itself can aggregate to form oligomers. Studies of wild-type p53 from mouse teratocarcinoma cells showed that p53 forms dimers, tetramers or multiple of tetramers[25]. Mutant p53 protein with altered conformation can self-aggregate and also form complexes with wild-type p53. In these complexes, mutant protein exerts a dominant negative action on wild-type protein, resulting in nonfunctional p53[87,88]. In some temperature-sensitive mutants, p53 is able to change its conformation. It can switch its conformation from wild-type at low temperatures (32°C) to mutant at high temperatures (37°C) and this change in conformation is accompanied by change in activity from a growth suppressor to a growth promoter[89–91]. Change in conformation of wild-type p53 can also be induced by chelating agents, suggesting that divalent cations (most probably Zn^{2+}) stabilize the tertiary structure of p53[90].

Ullrich *et al.*[7] showed that in human glioblastoma cell line containing an endogenous mutant p53 allele and an inducible wild-type allele, wild-type p53 exists in two pools. One pool is of complexed wild-type and mutant p53, in mutant conformation, and the second pool consists solely of free wild-type p53 in wild-type conformation. At G_1 arrest, the amount of wild-type p53 complexed with mutant p53 decreases and free wild-type p53 complex increases and phosphorylation/dephosphorylation plays an important role in this change in conformation[7]. Hyperphosphorylated form of p53 exhibits wild-type conformation and exerts an anti-proliferative effect. This change in conformation of wild-type p53 protein can also occur in the absence of mutant protein. Antisense p53 constructs were shown to be inhibitory to cell growth, suggesting that wild-type p53 plays an important role in cell growth[91]. In tumours the mutated p53 proteins are abnormally stabilized in a growth-promoting conformation which stimulate the cells to proliferate. The ability of mutant p53 to act in a growth promoter fashion suggests that it may be capable of acting on a different set of cellular targets than wild-type p53 to affect cell growth.

Based on these studies about change in conformation of p53, a model has been proposed[51] (Figure 4). According to this model, p53 exist in three states: (i) a latent or inactive state (composed of a higher-order multimer of p53; (ii) a suppressor state which mediates G_1 arrest and (iii) a promoter state which stimulates growth. The evidence of latent state for p53 was given by Hupp

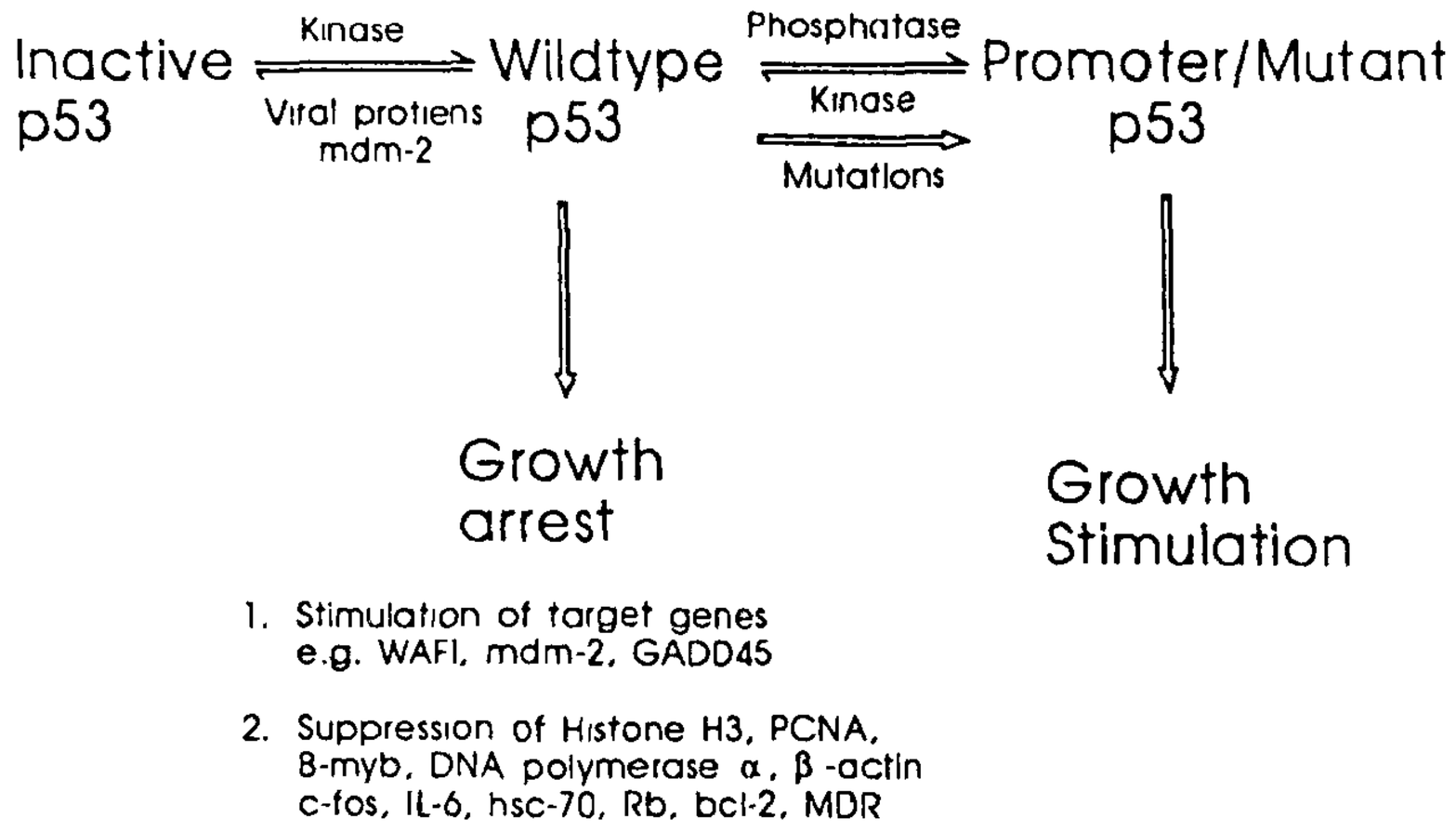

Figure 4. Conformational change of p53 with phosphorylation/dephosphorylation of the protein. Phosphorylation of the protein transforms it into wild-type, which activates and suppresses many genes to arrest the cells in G_1 phase. The dephosphorylation of wild-type leads to mutant or promotor conformation, which drives the cells into S phase.

et al.[92], who showed that full DNA binding activity was conferred on p53 only after cleavage or phosphorylation of C-terminal domain. In normal cells, p53 exists in inactive state and in response to stress (DNA damage) casein kinase II or other kinases phosphorylate p53 to induce G_1 arrest. After the removal of stress (DNA repair), C-terminal phosphate is removed by phosphatases and p53 achieves a growth promoter conformation. This promoter p53 helps to drive the cells into S phase before being degraded. Once into normal cell cycle, the need for either promoter or suppressor p53 decreases and inactive form predominates again.

Why does p53 fail in some tumours

The above study shows that p53 mutations are ubiquitous in tumours and the frequency of these mutations is 70% in colorectal cancers, 50% in lung cancers and 30–40% in breast cancers[11,15]. It means that still there are a fraction of tumours in which p53 mutations or allele losses have not been found; so why does wild-type p53 fail in those tumours. It has been found that in some of these tumours (breast tumours), p53 is localized in cytoplasm, showing that it is structurally altered in these cases; as a result, it cannot be translocated to nucleus[93]. Although the mechanism is unclear, possibility exists that mdm-2 oncogene product can bind to p53, making it functionally inactive. Phosphorylation/dephosphorylation could be another mechanism and, in some cases, p53-independent pathway of tumour progression (e.g. increased expression of myc) might have occurred[94,95]. Moreover, some of the mutations may occur in the noncoding region, with the result that the percentage of mutations determined is less.

Conclusions and future prospects

p53 protein monitors the integrity of host genome by acting upon DNA directly as well as through the regulation of other gene products, and this regulation (both positive and negative) is achieved by conformational change in its structure through phosphorylation/dephosphorylation. If the DNA is damaged, it arrests the cell cycle at G_1 to allow extra time for repair of damaged DNA and if the repair fails then it triggers the deletion of cells by apoptosis. In cells where p53 is mutated, uncontrolled cell proliferation leads to malignant tumours. These tumours are resistant to various anticancer agents like γ-radiation or chemotherapy because p53-dependent apoptotic cell death is absent in them[96]. The adenovirus-mediated transfer of wild-type p53 into p53-deficient tumours has led to their increased sensitivity to anticancer drugs in lung cancers[97] and head and neck cancers[98]. However, in tumours with an intact p53, it may be advantageous to combine chemotherapeutic agents (which induce p53-dependent apoptosis) with agents which arrest cells at G_1 or induce apoptosis via p53-independent pathway[47].

Although the work is in progress on the role of p53 in cell cycle regulation and apoptosis through transcriptional control of other genes, little is known about the signalling pathway involved in the regulation of p53 under normal as well as stress conditions. Also, it

remains to be elucidated how p53 protein monitors the balance between DNA repair and apoptosis.

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RESEARCH ARTICLES

A PC-based operational storm surge prediction system for disaster management in coastal India

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A storm surge prediction system has been set up at the Centre for Coastal Ocean Design and Prediction Systems (CODAPS), IIT, Madras, to test its validity as a reliable advance warning facility. The forecasting system, run on a personal computer, consists of a vertically integrated numerical surge model[1] driven by surface winds and quadratic bottom friction. The former is, in turn, computed from diurnal satellite meteorological data (preferably six-hourly) on the position of the cyclone centre, pressure drop and radius of maximum wind using the dynamic storm model developed by Jelesnianski and Taylor[2]. Within about 15 min the system generates two and three-dimensional temporal views of the estimated peak sea surface elevation along a desired stretch of the coastline about specified (anticipated) positions of the landfall.

The model simulates the actual curvilinear geometry of the shoreline with variable grid sizes, thereby providing finer resolution in the shallow seas of the eastern seaboard. It is also capable of simulating more realistic influence of coastal topography, whenever survey data become available.

EXTENSIVE inundation and flooding of low-lying coastal areas by sudden surges in the sea level raised by tropical storms is a recurrent cause of disaster along the Indian coast, particularly its eastern and northeastern seaboard (Figure 1). For, the Bay of Bengal, one of the warmest enclosed seas traversed by the seasonally migrating intertropical convergence zone, provides ideal conditions of high energy for their birth and development. Even though only about 7% of all the tropical cyclones that annually occur on the globe originate in the Bay of Bengal (Table 1), the toll of life and property exacted by them is proportionately rather large (Table 2). This is caused mainly by three factors. Firstly, over half of them intensify into severe storms with strong winds piling up sea water several metres high along the coast. Secondly, land levels along most of the Indian coast, particularly those occupied by extensive deltas, are low-lying so that even a few metres high surge leads to extensive flooding and landward incursion of the sea. Finally, the haphazard spread of the works and habitations of a burgeoning human family to every available ecological niche of the coastal ocean down to the shoreline makes them quite vulnerable to even moderate changes in the sea level.

In the past decade, of course, significant steps have been taken to provide advance warnings. For example, the existence of a network of coastal radars and satellite-based surveillance systems to track the evolution of cyclonic storms enabled the authorities to evacuate over 600,000 people to safe shelters in the wake of the 1990 Andhra cyclone which attained hurricane intensity. The death toll was thus limited to about 1000 compared to 20,000 killed by an earlier Andhra cyclone in 1977. In recent years, satellite-based early warning systems in Bangladesh have similarly helped to reduce the fatalities