p53: AN OVERVIEW

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ABSTRACT

Cancer is a family of diseases that exhibits uncontrolled cell division and tissue invasiveness (metastasis). The unregulated cell growth and metastasis are caused by mutations in the genes (DNA) of proteins involved in the regulation of cell cycle, and the agents causing DNA damage leading to subsequent transformation of a cell, are called carcinogens. Conventional chemotherapy has been the most common type of pharmacological anticancer treatment for decades. It never discriminates between rapidly dividing normal cells and tumor cells, thus leading to severe systematic side effects. In the last decade, the use of Novel Molecular Targeted therapies has raised immense interest due to lack of serious side effects as they inhibit specific molecules that have a role in tumor growth or progression, and not the normal cells. Hence, there is a need to understand some eminent molecular mechanisms of cancer for better clinical approach. Proto-oncogenes are normal genes that promote cell growth and mitosis, whereas Tumor Suppressor genes discourage cell growth. Proto-oncogenes can be mutated by carcinogenic agents to become oncogenes, genes producing excessive levels of growth promoting proteins. Tumor Suppressor gene products like p53 frequently suppress mitosis and cell growth to allow for DNA repair. These gene products can also be mutated by carcinogenic agents. Thus, cancer results from cumulative mutations of proto oncogenes and suppressor genes which together allow the unregulated growth of cells. However, both copy of a suppressor gene need to mutate to cause loss of suppressor function. Only one copy of a proto-oncogene needs to mutate for gain of function. Mutations of tumor suppressor genes can be inherited. Different mechanisms leading to continuous growth include, modulations of different stages of cell cycle, mutations in extracellular receptors/ pathways like JAK-STAT pathway, or intracellular signal transducer like the EGF receptor and Ras, DNA damage response due to inhibition or inactivation of transcription factor-p53, and proteins like ATM and ATR, epigenetics (direct modification of DNA), modulation of micro RNA (miRNA), chromthripsis (a catastrophic phenomenon), etc. Understanding of these mechanisms provides some novel procedures to target cancers like prostate cancer, breast cancer, blood cancer, bone cancer, lung cancer, and many more in a more efficient manner. Further, applying our knowledge about Molecular Mechanisms of Cancer in therapies represents an integrative approach to cancer therapy that has already led to important clinical results.

Keywords: p53, Cancer, TP53 gene, Tumor suppressor p53.

INTRODUCTION

Somatic mutations produce oncogenes or affect the functions of tumor suppressor genes, which augment the chances of uncontrolled proliferation and invasion of cells, leading to cancer [1, 2]. With the better insight about malignant transformation of cells, it has been easy to elucidate that tumor progression is a multistep process which involves several defined events common to cancer cells [1, 3]. Genes, controlling cell cycle events limit cell multiplication by activation of anti-proliferative mechanisms which leads to arrest of cell cycle or apoptosis. Mutations of these genes lead to autonomous cell growth. This, along with metastasis adds more aggression to the armoury of cancer. In the race of finding medical artillery to kill cancer, Science discovered a very crucial gene in the body, later named as, 'TP53 gene'. Like the drugs which reduced the ascetic fluid volume were seen as a good anticancer agent and thus purveyed a new technique for targeting cancer [4], emergence of TP53 gene provided a whole new arsenal to combat cancer. The p53 protein, coded by TP53 gene, is an inducible transcription factor that plays multiple anti-proliferative roles in response to exposure to DNA damaging stress.

In physiological context, condition of p53 controls the sensitivity of cells to environmental mutagens. In pathological context, the status of p53 is considered as a key factor in response of cancer cells towards cytotoxic therapies. Thus, p53 functions for the genetic homeostasis of the cells exposed to mutagens [5].

DISCOVERY AND HISTORY

In 1979, L. Crawford, D. Lane, A. Levine, and L. Old, identified p53. In 1982, Peter Chumakov was the first to clone the TP53 gene from mouse [6], while the human TP53 gene was cloned in 1984[7] . It was hypothesized to exist as the target of the SV40 virus, a strain that induced development of tumors. Initially presumed to be an oncogene, its character as a tumor suppressor gene was finally revealed in 1989 by B. Vogelstein [8]. In 1993, p53 was voted molecule of the year by Science magazine. In the same year, Wafik El-Deiry, working with Bert Vogelstein at Johns Hopkins University discovered that a gene, p21 (WAF1), was directly, regulated by p53. This work provided a molecular mechanism by which mammalian cells undergo growth arrest when damaged [9]. Binding of the p53 protein to the major oncogenic protein of SV40, strongly suggested that it was a downstream effecter of the large T-antigen pathway. The interpretation was consistent as high levels of expression of p53 were found in many cancers and so p53 was originally believed to be an oncogene [10]. In 1989, during a search for a putative tumor suppressor gene on chromosome 17p, p53 containing region came into focus. Researchers applied a "two-hit" test to distinguish whether a mutant gene is an oncogene or a tumor suppressor gene. The logic behind this "two-hit" test being, if both copies of the gene are altered, it is likely to be a tumor suppressor gene; if only one copy is altered, it is more likely to be an oncogene. When p53 went through this test, the results were very astonishing. The majority of colorectal tumors were surprisingly found to have subtle mutations of p53, generally a single base substitution (such as C to T) resulting in a new amino acid. Also, virtually in all cases, both copies of p53 were mutated. One copy was generally altered by a base substitution, while the other was often completely deleted from the cell. This result was expected for a tumor suppressor gene, and not for an oncogene. This "two-hit" test was later applied to many other tumor types and every-time a similar result was found. Thus, bringing p53 into the center stage of human tumor research, and providing with the evidence that p53 was actually a tumor suppressor gene. Subsequent findings concluded that, patients with inherited mutations of p53 were predisposed to diverse tumor [11]. Studies have demonstrated that p53 is the most frequently mutated gene in human tumors than any other gene in the genome [12].

NOMENCLATURE

The name 'p53' comes from the apparent molecular mass of the protein. On SDS-PAGE, it runs as a 53-kilodalton (kDa) protein, but, based on calculations from its amino acid residues, p53's molecular mass is actually only 43.7 kDa. This difference in molecular mass is due to the high number of proline residues in the protein, which slows its migration on SDS-PAGE, thus making it appear heavier than it actually is [13]. This effect is observed with p53 from other species too, including humans, rodents, frogs, and fish.

Other Names

- UniProt name: Cellular tumor antigen p53
- Antigen NY-CO-13
- Phosphoprotein p53
- Transformation-related protein 53 (TRP53)
- Tumor suppressor p53

GENETIC MAKE-UP

In humans, the TP53 gene is located on the short arm of chromosome 17 [14, 15, 16, 17].Human p53 is a nuclear phosphoprotein of molecular weight- 53 kDa, encoded by a 20-Kb gene which contains 11 exons and 10 introns [18] .The coding sequence contains five regions which shows a high degree of conservation in vertebrates, predominantly in exons 2, 5, 6, 7 and 8, but the sequences found in invertebrates show only distant resemblance to mammalian TP53 [19] .In humans, a common polymorphism involves the substitution of an arginine for a proline at codon position 72, indicating a possible cancer susceptibility, however, the results have been controversial. For instance, a meta-analysis from 2009 failed to show a link for cervical cancer, while a 2011 study found that the TP53 proline mutation had a profound effect on pancreatic cancer risk among males [20, 21] . A study of an Arab women found that proline homozygosity at TP53 codon 72 is linked with a decreased risk for breast cancer [22]. A 2011 study concluded that the polymorphism of TP53 codon 72 was associated with an increased risk for lung cancer [23]. In 2011, meta-analyses studies indicated that no significant associations existed between TP53 codon 72 polymorphisms and both colorectal cancer risk and endometrial cancer risk [24, 25] .

STRUCTURE

Human p53 is 393 amino acids long and has seven domains:

1. An acidic N-terminus Transcription Activation Domain (TAD), also known as Activation Domain 1 (AD1) [residues 1-42], activates transcription factors. The N-terminus contains two complementary transcriptional activation domains, with a major one at residues 1–42 and a minor one at residues 55–75, specifically involved in the regulation of several pro-apoptotic genes [26].
2. Activation Domain 2 (AD2) [residues 43-63] is important for apoptotic activity.
3. Proline rich domain [residues 64-92] is important for the apoptotic activity of p53.
4. Central DNA-Binding core Domain (DBD) [residues 102-292], containing one zinc atom and several arginine amino acids, is responsible for binding the p53 co-repressor LMO3[27].
5. Nuclear localization signaling domain [residues 316-325].
6. Homo-oligomerisation domain (OD): residues 307-355. Tetramerization is essential for the activity of p53 in vivo.
7. C-terminal [residues 356-393] is involved in down-regulation of DNA binding of the central domain [28].

P53 PATHWAY AND ITS REGULATION

p53 plays a significant role in apoptosis, genomic stability and inhibition of angiogenesis. It also executes anticancer function by the virtue of different mechanisms as follows:

- Activation of DNA-repair proteins when DNA suffers damage.
- Instigates growth arrest by holding the cell cycle at the G_1/S regulation point, thus giving ample time to the DNA-repair proteins to fix the DNA damage, and subsequent continuation of the cell cycle.

Initiation of apoptosis, the programmed cell death, if incase, the DNA damage proves to be irreparable.

p53 exists in inactive state in normal cells due to the presence of its negative regulator, mdm2. However, on DNA damage (by ionizing radiation, UV radiation, application of cytotoxic drugs or chemotherapeutic agents, and infectious virus) or other stresses such as heat shock, hypoxia, oxidative stress, osmotic shock, ribonucleotide depletion, and deregulated oncogene expression, p53

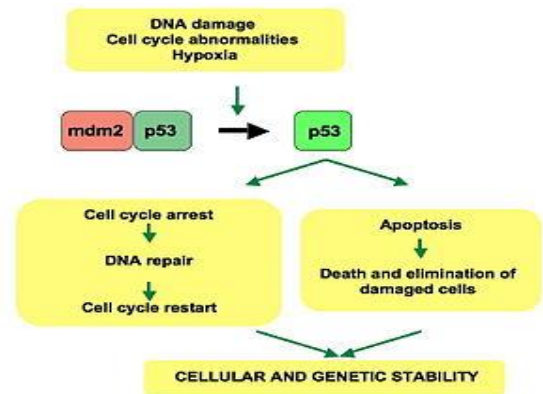dissociates from mdm2 and this dissociation of the p53 from mdm2 complex leads to activation of p53[29]

Fig. 1: Flow-chart showing activation and functions of p53

Two major events causing the activation of p53 can be highlighted as follows:

- Drastic increment in the half-life of the p53 protein, leading to a its accumulation in stressed cells.
- A conformational change forcing p53 to be activated as a transcription regulator in these cells.

Phosphorylation of N-terminal domain marks the activation of p53. Several protein kinases that target phosphorylation sites present in large numbers in the N-terminal transcriptional activation domain of p53, can be roughly divided into two groups. First group comprises of protein kinases belonging to the MAPK family (JNK1-3, ERK1-2, p38 MAPK), which is known to respond to several types of stress including, membrane damage, oxidative stress, osmotic shock, heat shock, etc. while, the second group includes protein kinases (ATR, ATM, CHK1 and CHK2, DNA-PK, CAK, TP53RK) involved in the molecular cascade that detects and responds to several forms of DNA damage caused by genotoxic stress. Oncogenes also stimulate p53 activation, mediated by the protein p14ARF. Marked enhancement is observed in p53's sequence-specific DNA binding and transcriptional activities towards stress, due to numerous post-translational alterations within the carboxy terminus. These alterations include phosphorylation, acetylation and sumoylation [30,31,32,33].

In unstressed cells, p53 is continuously degraded. A protein called Mdm2 (also called HDM2 in humans), a product of p53, binds to p53, and renders it inactive. Mdm2 carries out the transportation of p53 from the nucleus to the cytosol, apart from acting as ubiquitin ligase and carrying out reversible attachment of ubiquitin to p53 for its further degradation by the proteasome. Proteosome-dependent degradation of p53 can be shunned by use of ubiquitin specific proteases like, USP7 (or HAUSP), USP42, capable of cleaving ubiquitin off p53. HAUSP, which has been shown to be a better binding partner to Mdm2 than p53 in unstressed cells, is mainly localized in the nucleus, though a fraction of it have been found in the cytoplasm and mitochondria too [34]. USP10 located in the cytoplasm in unstressed cells also performs the same function of reversing the ubiquitination of Mdm2. On DNA damage, USP10 translocates to the nucleus and executes its activity without any interaction with Mdm2 [35].

On activation, p53 may either account for cell-cycle arrest for repairing the DNA damage or it may carry out apoptosis to discard the damaged cells. Active p53 binds to DNA and activates several genes including microRNA miR-34a, WAF1/CIP1 encoding for p21 and hundreds of other down-stream genes, to express themselves [36]. p21 (WAF1) binds to the G1-S/CDK (CDK2) and S/CDK complexes, essential molecules for the G1/S transition in the cell cycle. p21 (WAF1) is when gets associated with CDK2, the cell fails to progress into the next stage of cell division. It is important to note that, a mutant p53 will not bind to DNA in an effective manner,

and, as a result, the p21 protein will not be available to act as the "stop signal" for cell division [37]. 50% ethanolic extract of Chios Mastic Gum (CMG) of *Pistacia lentiscus* was found to be working like p53 in inhibiting proliferation and inducing death of HCT116 human colon cancer cells in vitro, by exerting concentration dependent apoptosis through direct or indirect induction of cell arrest at G1phase followed by DNA damage[38].

Some of the above-mentioned protein kinases phosphorylate the N-terminal end of p53, causing the disruption of Mdm2-p53 binding. This is then followed by recruitment of other proteins like, Pin1, to induce a conformational change in p53, preventing the Mdm2-p53 binding even more. Phosphorylation of the N-terminal end allows for binding of transcriptional coactivators, like p300 or PCAF, which are essential for the acetylation of the carboxy-terminal end of p53. Thus, exposing the DNA binding domain of p53, and imparting it with the ability to activate or repress specific genes. On the other hand, deacetylase enzymes, such as Sirt1 and Sirt7, can deacetylate p53, resulting into an inhibition of apoptosis [39]. In the nutshell, it can be stated that p53 is a transcriptional activator, which regulates the functioning of several genes. Some important examples can be listed as follows:

1. Growth arrest: p21, and Gadd45
2. DNA repair: p53R2.
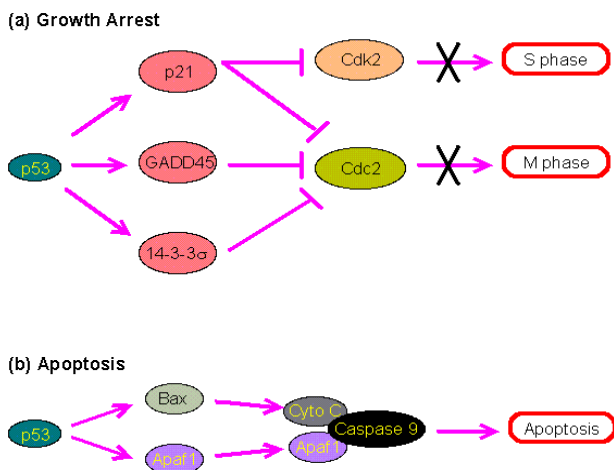3. Apoptosis: Bax, Apaf-1, PUMA and NoxA [40].

Fig. 2: p53, a transcriptional activator

a) Growth arrest:-The enzyme Cdk2, essential for the cell cycle progression into the S phase, can be inhibited by p21. Similarly, progression into the M phase requires Cdc2 which can be inhibited by p21, or GADD45. p53 by regulating the expression of these inhibitory proteins induces growth arrest.

b) Apoptosis:-p53 activates the expression of Apaf1 and Bax. Bax stimulates the release of cytochrome c, which alongwith Apaf1, acts as the binding site for Caspase 9. Caspase 9 induces apoptosis. Thus, p53 contributes to apoptosis [41].

ROLE IN DISEASE

It is obvious that, tumor suppression ability will be severely jolted if the TP53 gene is damaged. Chemicals, radiation, viruses or other mutagens, may damage the TP53 gene, thus increasing the probability of uncontrolled division of cells, if any oncogenic mutation enters in the genetic make-up of an individual. A disease known as Li-Fraumeni syndrome, exhibits one such situation where tumors develop early during adulthood due to inheritance of only one functional copy of the TP53 gene. More than 50 percent of human tumors are caused due to mutation or deletion of the TP53 gene [42].

Approximately, 95% of TP53 mutations have their roots in the DNA binding domain, reflecting the fact that transcriptional activation is a key role exercised by the gene. Majority of these mutations include a single amino acid change in the core domains, indicating point mutations [43]. These point mutations have been classified into structural and DNA contact; where former can destabilize p53 protein, while the latter class directly interferes with residues involved in DNA binding [44].

Hence, endogenous p53 functioning is an important cog in the wheel, in order to combat tumor growth [45]. Also, the understanding that, an excess amount of p53 may prove to be a boon, was thrashed by the fact that, the excess amount can actually cause premature aging [46]. On the other hand, loss of p53 creates genomic instability, which most often results in having a chromosome number that is not an exact multiple of the haploid number, a condition known as, aneuploidy [47]. In certain cases, TP53 gene is not mutated, but the p53 pathway is disturbed. One such example of destabilizing p53 pathway is increased expression of mdm2 and mdm4, the negative regulators of p53 [48,49]. Also, deletion or epigenetic inactivation of ARF, a negative regulator of mdm2, and known as p14[ARF] in human beings, accounts for destabilization of p53 pathway [50,51].

Apart from the gene, even the protein expressed by TP53 can get affected leading to abnormal conditions. Pathogen, human papillomavirus (HPV), encodes a protein, E6, which when binds with the p53 protein, causes its inactivation. This, in conjunction with the inactivation of another cell cycle regulator, pRb, by the HPV protein E7, allows for repeated cell division manifested in the clinical disease of warts [52].

Table 1: Mechanisms of inactivation of p53 and the subsequent effects [53].

Mechanism of inactivating p53	Effect of inactivation	Typical tumors
Amino-acid changing mutation in the DNA-binding domain	Prevents p53 from binding to specific DNA sequences and activating the adjacent genes	Colon, breast, lung, bladder, brain, pancreas, stomach, oesophagus, and many others
Deletion of the carboxy-terminal domain	Prevents the formation of tetramers of p53	Occasional tumors at many different sites
Multiplication of the MDM2 gene in the genome	Extra MDM2 stimulates the degradation of p53	Sarcomas, brain
Viral infection	Products of viral oncogenes bind to and inactivate p53 in the cell, in some cases stimulating p53 degradation	cervix, liver, lymphomas
Mislocalization of p53 to the cytoplasm, outside the nucleus	Lack of p53 function(p53 functions only in the nucleus)	breast, neuroblastomas

TARGETTING P53

More than 50% cancers involve mutations in TP53 gene, this itself underlines the fact that TP53 gene or even p53 protein can provide a link to treat cancer in many cases. Hence, targeting TP53 or p53 is important clinically.

I. Gene therapy

Loss of potency of TP53 has led to the occurrence of many cancers. Hence, restoration of p53 functioning by replacing the mutant gene with a functional wild-type copy, seemed to be an exciting approach towards the targeting of p53. This exciting approach is utilised and executed by Gene therapy, which in turn, depends upon the efficient delivery of the wild-type TP53 into tumor cells in vivo. Scientists have also proposed various in vitro strategies to restore the tumor suppressing function of p53 in cancer cells.

TP53-gene therapy mediated by Retrovirus

Retroviruses, by the virtue of their unavoidable qualities of getting integrated in a stable form into the genome of infected cells and

requiring cell division for the transduction, pose to be an obvious candidate for gene therapy. Retrovirus-mediated gene transfer of the wild-type TP53 gene into both human lung tumor cell lines and xenograft models has been shown to inhibit the tumor cell growth [54-56]. So far, no molecule has induced biological response, but it is believed that some may prove to be lead compounds for more biologically active agents, when processed further. A promising target for anti-cancer drugs is the molecular chaperone Hsp90, which interacts with p53 in vivo [57].

TP53-gene therapy mediated by Adenovirus

Unlike retrovirus, adenovirus effect is not limited to actively proliferating cells. Hence, these large, double-stranded DNA viruses capable of high transduction efficiency form a second strategy to TP53 gene replacement therapy [58]. Adenoviruses, by secreting certain proteins, compel the host to replicate them. Due to their inability of not getting integrated into the genome, adenoviruses exhibit no risk of insertional mutagenesis. In the 1960s, oral adenoviral vaccines were given to thousands of military recruits without increase in cancer risk [59].

II. Killing p53-deficient cells

This approach involves the introduction of genetically modified viruses that exploits the advantage of dysfunctional p53 in cancer cells to selectively kill them. Adenoviruses infect quiescent cells and induce them to enter the S phase of the cell cycle so that viral DNA replication can proceed [60].

ONYX-015 (dl1520, CI-1042) is a modified form of adenoviruses, obtained from a virus that expresses the early region protein, E1B, which binds to p53 and inactivates the same. In ONYX-015, E1B region has been deleted. P53 suppression is necessary for the virus to replicate, hence it selectively replicates in p53-deficient cancer cells but not in normal cells [61]. It was hoped that the viruses would select tumor cells, replicate and spread to other surrounding malignant tissue thus increasing distribution and efficacy. However, clinical trials of ONYX-015 have been unsatisfactory, except when the virus was used in combination with chemotherapy. One of the reasons for the disappointing results of the clinical trials can be the fact that E1B has other functions which are vital to the virus, or due to extensive fibrotic tissue causing hindrance to virus distribution around the tumor [62].

III. Modification of p53 protein functions

- p53 activation

Accumulation of wild-type p53 can be achieved by disrupting the negative regulation by mdm-2. Mdm-2 gene contains a p53-responsive element within itself to which p53 binds, thus causing transcriptional activation of the protein mdm-2. Mdm-2 binds to the N-terminus of p53, and prevents p53 from interacting with the transcriptional machinery and induces its degradation by the proteasome. In 1997, Bottger et al. designed a synthetic mdm-2-binding mini-protein that specifically targets the p53-binding site [63]. Certain synthetic polyamines analogues have also been shown to activate p53 function in a number of cultured cell lines [64,65].

- p53 inhibitors

Pifithrin, a synthetic compound, rescues p53 cells from apoptotic death induced by irradiation and various cytotoxic drugs including doxorubicin, etoposide, paclitaxel and ara-C [66]. Thus, pifithrin may be used to suppress the side effects of radiation therapy or chemotherapy in cancer patients. However, pifithrin could act as an activator of the p53 pathway promoting doxorubicin-induced apoptosis in mouse epidermal JB6 C141 cells [67].

- Re-activation of wt-p53 activity in mutant p53

Some mutants totally lose wild-type p53 function, while some are not associated with irreversible loss of wild-type activity. The sequence-specific DNA-binding, a key biochemical activity of p53, is altered by mutation. This activity is regulated by two C-terminal domains (residues 325–363) and negative control of DNA-binding (residues 363 393). Inhibition of the latter domain is crucial for high-affinity binding to DNA. Several experimental studies have shown that it is possible to target this domain specifically with peptides or proteins that neutralize the negative regulation exerted by the extreme C-terminus [68].

p53 deficient cells when subjected to in-vitro introduction of p53, exhibits a rapid death of cancer cells or prevention of further cell division [69]. Apart from guarding the cell from various stress signals other functions of p53 in suppressing the tumors have been identified. These include, direct effects on survival proteins in the mitochondria [70,71], regulation of microRNA processing [72] and involvement in dNA repair pathways [73].

Table 2: Strategies and mechanisms for small molecules that target the p53 pathway

Molecule	Mechanism of action	Stage in clinical testing
Reactivate mutant p53		
PRIMA-1	Protein folding[74]	Phase I(APR-246)
CP-31398	Protein folding[75]	Preclinical
PhiKan083	Protein thermal stability[76]	Preclinical
Activate wild-type p53		
Nutlin	MdM2 binding[77]	Phase I
MI-219	MdM2 binding[78]	Phase I
Tenovin-6	SIRT1 and SIRT2 inhibition[79]	Preclinical
RITA	p53 binding[80]	Preclinical
Leptomycin B	CRM1 binding[81,82]	Phase I (Elactocin; withdrawn[82])
Actinomycin d	RPL11 and RPL5 release[83]	Approved (dactinomycin)
Cyclotherapy (temporal combination of p53 activator and mitotic inhibitor)		
Nutlin*	BI-2536 (PLK1 inhibitor[84])‡	Phase I/Phase I§
Nutlin*	VX680 (Aurora inhibitor‖)‡	Phase I/Phase I§
Tenovin-6*	Taxol (Tubulin binding[85])‡	Preclinical/approved§
Actinomycin d*	Taxol‡	Approved/approved§

*p53 activator. ‡ Mitotic inhibitor. §Combinations are not in trial together or have been approved together. ‖d.L.P., unpublished

observations. CRM1, exportin 1; PLK1, polo-like kinase 1; RITA, reactivation of p53 and induction of tumor cell apoptosis; RPL, ribosomal protein L; SIRT, sirtuin.

Drug combinations

According to a recent report, combination of CDK inhibitors (Roscovitine and DRB) and nutlin-3 showed synergistic effect not only in the activation of p53, but also in the apoptosis of p53 wild-type tumor cells.

Apart from retaining the non-genotoxic nature characteristic of the individual compounds, the combination also confirms the concept that combinations of low doses of individual compounds which are not sufficiently dose potent on their own are effective in inducing the desired outputs. However, determination of a fixed ratio of the compounds and formulating them so as to work optimally together

taking into account the variable P_K and P_D properties of the individual molecules, is a barrier in designing these drug combinations [86].

p53 VACCINES

Marked increment in the growth of tumors in an immune-suppressed individual indicates a possible role of weakened immune system in cancer. Thus, the immune system can be extremely effective in controlling tumor growth. In model systems using virally transformed cells, small numbers of cytotoxic T cells can completely control tumor growth by recognizing the peptides displayed on the surface of the tumor cell through the MHC system [87].

However, due to the absence of 'tumor specific antigens', tumor immunity looks ineffective against continuosly expanding tumors in man. Inorder to establish tumor-specificity, it is important that immune system distinguishes self from nonself, effectively. This can be achieved with the help of regulatory T cells in the periphery [88].

p53, present in the tumor cells may be considered "nonself" or tumor specific because the tumor specific mutations present in the p53 protein may alter its antigenicity, if the mutations occur in a region of the protein that can be presented as an epitope to the T cell; and also because of its universal nature, the p53 protein in tumor cells accumulates to high levels implying that it is subject to different processes of degradation, which in turn may lead to the production of different peptide fragments to those that result from the processing of p53 in normal tissue cells, thus easy and specific identification by T- cells. Currently, varieties of p53-based vaccines have proved effective in animal models and are now undergoing trial in man. Key p53 peptide epitopes have been discovered [89, 90].

CONCLUSION & FUTURE OF P53

An age-old thinking that cells accumulate a succession of genetic modifications accompanied with an increase in the aggressiveness of the tumor needs to be disbelieved now. p53 gene alone might be implicated in both control of proliferation and control of cell migration. Consequently, no specific genetic changes can be exclusively associated with invasiveness, due to their participation in the formation of primary tumors.

The question whether the internal domains of p53 which are important for its function, overlap with those necessary for its anti-proliferative properties is yet to be answered. It would certainly provide an insight into the manner in which p53 essays its two roles, anti-proliferator and cell migration regulator. Also, further studies are necessary to comprehend and confirm whether the role of p53 in cell migration influences metastatic development in human cancers. It will ascertain the relative contributions of each of the functional properties of p53, i.e. control of cell cycle, apoptosis and cell migration, in tumorigenesis. More work needs to be done to uncover the excitement surrounding the existence of gene exclusivity associated with primary tumor formation with no effect on cell migration. The outcome of these studies can provide a novel and promising anti-cancer therapeutic approach [91].

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