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Review Article

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p53 AND CANCER

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ABSTRACT

The p53 gene located in human chromosome 17, suspends the cell cycle when there is DNA damage. If there is a mutation in p53, the cell cycle continues unrestrained and reproduces the damaged DNA, leading to uncontrolled cell proliferation and cancer tumors. The p53 protein is a transcription factor and its pivotal role in maintaining genomic integrity has earned it the nickname "guardian of the genome". p53 gene is mutated in about 50% of human cancers of breast, colon, lung, liver, prostate, bladder, and skin. Since the loss of p53 function is so prevalent in human cancer, this protein is an ideal candidate for cancer therapy. Several gene therapeutic strategies have been employed in the attempt to restore p53 function to cancerous cells.

Keywords: p53gene, p53 protein, Tumor suppressor gene, Mutation, Cancer therapy.

INTRODUCTION

The p53 gene was discovered by Arnold Levine, David Lane and William Old in 1979. Earlier it was considered to be an oncogene but later it was cloned and characterized as the tumor suppressor gene. P53 is the most commonly varied gene in human cancers. These mutations often cause conformational changes of the p53 protein, which consequently impairs the capacity of DNA binding, which results in the loss of p53 function and reduced sensitivity to apoptosis or senescence, a permanent status of irreversible cell cycle arrest. [1]

Furthermore, these conformational changes often alter the p53 protein resulting in raising the p53 level in tumors, which is frequently used as a surrogate marker of p53 mutation.

TP53 holds its uniqueness among cancer genes in three ways:

- Generally, the alterations in cancer are missense mutations. This is not very common for suppressor genes, which are inactivated by deletions or non- sense mutations.
- It is altered at a particular frequency (between 20 and 80%) in almost every human cancer, irrespective of the organ site or the histological type.
- The protein itself is reasonably essential for many aspects of normal life. This also contrasts with many tumor suppressors, which encode important proteins.

Therefore, the function of p53 is mainly to guard cells against the occurrence and development of cancer and also as explained by M. Oren, the "ultimate tumor suppressor gene"

Trp53 is a master transcription factor which regulates the expression of a plethora of genes involved in the crucial biological processes, many of which encipher proteins that control the cell cycle or induce apoptosis. Because of its critical impact on cell predestination, cellular p53 activity must exactly be controlled. It was first thought to be an ontogeny, but 10 years later researchers Bert Vogelstein and Ray White, who then studied colon cancer, showed p53 to be a tumor suppressor gene. In the past over the period of 10 years, the roles of p53 in human cancers have been investigated widely in many aspects.

P53 gene is not responsive in cells where DNA is undamaged. When there is damage in the DNA, the gene suspends the cell cycle until the injury can be repaired. If there is a mutation in p53, the cell cycle continues uncontrolled and reproduces the injured DNA, leading to unrestrained cell proliferation and cancer tumors. Cancer results as the cell with destroyed DNA divides, this DNA is replicated and each daughter cell's cycle is also uncontrolled. [2]

All cancer cells contain mutagenesis in combinations of tumor suppressors and ontogenesis. The removal of functional p53, from a cell allows for the accretion of even more DNA damage and the division of cells that contain damaged DNA. The mutation of p53 is one of the most regular genetic changes seen in cancer cells. In addition to mutations that arise during the growth and advancements of individuals (sporadic mutations), there are forms of cancer associated with the acquisition of a damaged version of p53. In addition, several viruses have developed ways of inactivating the p53 protein.

The p53 gene

The Chromosomal Location of p53 genesis: 17

The p53 gene encompasses 20kb of DNA with 11 exons which on transcription gives a 3.0kb mRNA having 1179bp open reading chase. On translation, this mRNA produces a 53kDa protein (hence the name p53)

This very special position of p53 in the control of cell maturation is due to two biological characteristics. First, p53 is a protein which is inducible at the post- transcriptional level. It is almost absent, or "latent," in most standard cells and tissues, but becomes steady and actuated in response to many forms of cellular stress, in particular stress generating the formation of DNA-damage. Moreover, p53 is capable of limiting many overlapping pathways. P53 is a transliteration factor with more than 30 known target genes in pathways such as cell cycle control, apoptosis, DNA repoint, contradistinction, and senescence. The protein also acts through direct, convoluted formation with other cellular constituents, further increasing the range of responses elicited by p53 activation. Overall, p53 radiates to sit at the midstream of a reticulum of signals that connect stress response (in particular to DNA damage) with growth regulation. This special function has attained p53 the nickname of "guardian of the genome". Loss of p53 function thus eliminates over shielding system by which cells usually adjust their capacity to proliferate in stressful conditions, and increases the probability that such cells may acquire other transmissible changes during cancer progression. [2]

The p53 protein (p53)

The p53 protein is a combination of 393-residue polypeptide and form N- terminal to C-terminal. It contains five functional domains.

1. N-terminal preserve (residues 1-43) that are involved in transcriptional activation.
2. A Proline rich preserve (63-97) and Mdm2 binds to both these domains.
3. The large, central core domain (residues 100-300) that involves in DNA binding, and is the region of almost all oncogenic p53 transposition.
4. The oligomerization domain (residues 320-360) contains nuclear determined signals and is involved in p53 tetramerization.
5. The basic C-terminal preserve (residues 364-393) is a negative regulatory domain that can suppress sequence-specific DNA binding by the core domain.

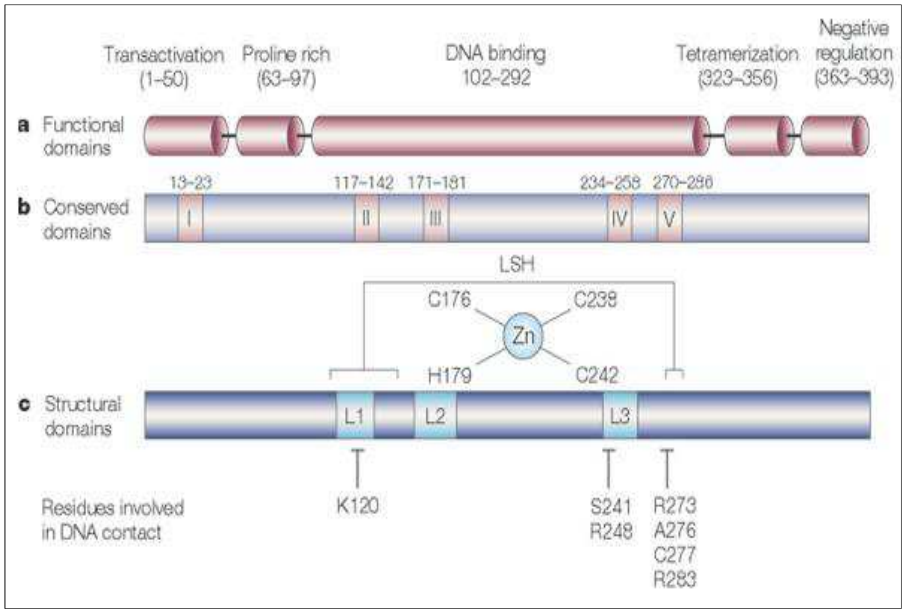

Fig 1: p53 protein-TP53 [1]

Features of p53 protein

1) Cofactor**:** Binds 1 zinc per subunit.

2) Subunit**:** Binds DNA as a homotetramer.

Cellular roles of p53

I. The transmission of destroyed genetic information from one cell generation to the next is obviated by p53. It does this by binding to a transliteration factor called E2F.

II. p53 prevents E2F from binding to the advertizers of proto- oncogenes such as *c-myc* and *c-fos*. Transliteration of *c-myc* and *c-fos* is needed for mitosis to blocking the transliteration factor which is needed to turn on these genes to avoids cell division.

III. Initiates apoptosis if the damage to the cell is intense and works as an emergency brake on cancer advancement by killing cells that attempt to proliferate in oxygen-deficient regions of tumors.

IV. Alteration in p53 can cause cells to become *oncogenically transformed,* and transfection studies have shown that p53 act as a powerful trans-dominant tumor suppressor that some level of normal growth to cancerous cells *in vitro*.

V. p53 is a powerful transcription factor and once activated, it represses transcription of one set of genes (several of which are implicated in stimulating cell growth)

VI. The function of p53 is critical to the way that many cancer treatments decapitate cells since radiotherapy and chemotherapy act in part by triggering cell suicide in response to DNA damage.

p53- Activating Signals

It does not interfere with cell cycle progression and cell survival. p53 is not essential for the normal representation of cells within the body. A variety of conditions can lead to rapid induction of p53 activity, which corresponds to 5 types of stress, that are likely to favor the emergence of cancer bound cells. Such conditions includes direct DNA damage as well as damage to the divisions involved in the proper handling and segregation of the cellular genetic materials (eg. The mitotic spindle piece, ribo-nucleotide depletion, hypoxia, heat shock, and vulnerability to nitric oxide (NO).

The p53-Mdm2 Loop

The p53 level is controlled by its inhibiter molecules, Mdm2 (Mouse double minute 2 homolog). Mdm2 is the major controller of p53 stability and prevents it from binding to the promoter and also actively contribute the fast abasement of p53. Mdm2 is the product of an oncogene, whose excess activity alleviates various types of human cancer. [3]

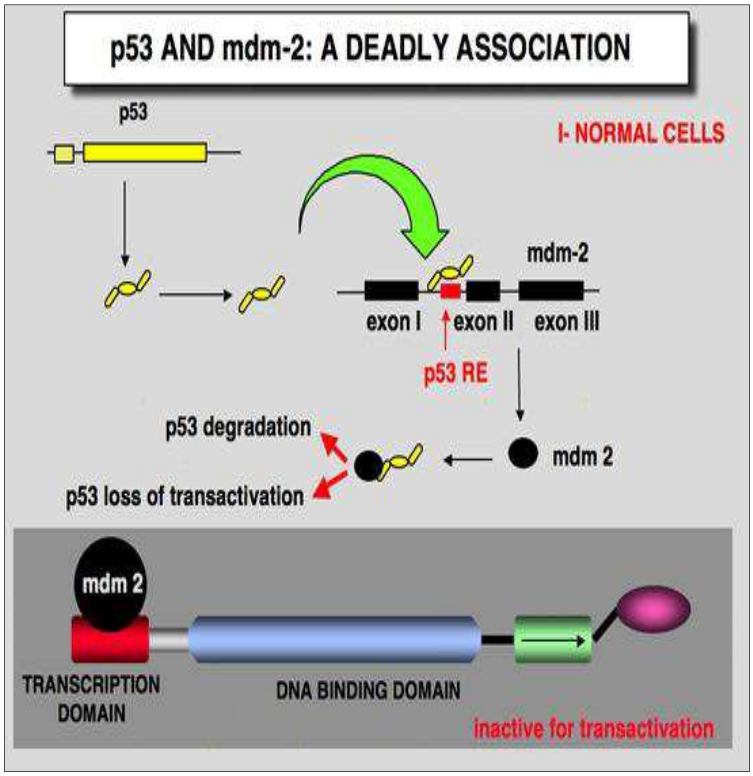

Fig 2: p53 and MDM2 association [3]

A key player in the ordinance of p53 is the Mdm2 protein. Mdm2 exhibits a unique relationship with p53. On the other hand, the Mdm2 protein binds to p53 and makes it inactive. The binding occurs right within the p53 transactivation domain, interfering with arrangement of basal transcription machinery components.

When a cell suffers from DNA damage by genotoxic, chemotoxic stress or gets abnormal signals from oncogene activation, p53 is activated causing an elevated level of p53 correlated with its two components, acetylation and phosphorilation.

Recent emerging evidence reveals that p53 can also be activated by different physiological and pathological stressors, which include hypoxia, metabolic stress, ribosomal stress, nutrient deficiency, viral infection, endoplasmic reticulum (ER) stress, and psychological stress.

Thus, as a crucial sensor of cellular stress, p53 plays a significant role in ensuring proper health and function of all cells by dictating that how processes like apoptosis, senescence, or transient cell cycle arrest will occur, depending on the level and nature of the stress that the cells encounters as well as to see how severe it is damaged and whether the damage can be reversed Though severe stress and un-repairable damage results in apoptosis or senescence and modest stress. The repairable damage results in transient cell cycle arrest. Cells will re-enter the cell cycle to produce progeny as soon as the damage in the DNA is repaired.

The well regulated induction of apoptosis or senescence is the major mechanism through which p53 suppresses tumor development and ensures stability of the genome. Therefore, p53 is considered to be the caretaker, gatekeeper, and guardian of the genome.

P53 Mutations and Human Cancer

Therefore, p53 represents an interesting target for genetic or pharmacological involution in cancer treatment. Below, we briefly review the deduction of TP53 in human cancer, and we describe current approaches for cancer

gene therapy, the P53 protein is pharmacologically modulated, and exploitation of TP53 in cancer detection and monitoring.

The functional P53 molecule is in tetrameric form and functions as a transcriptional factor. It is involved in cell cycle checks, senescence, genomic unreliability, and DNA repair.

The protein in Figure 3 contains various functional preserves, as indicated. The number of mutations detected in the human cancer that falls within each of this environment is given. The most frequently mutated portion is the sequence-specific DNA-binding domain. Within this environment several residues are "hotspots" for mutation.

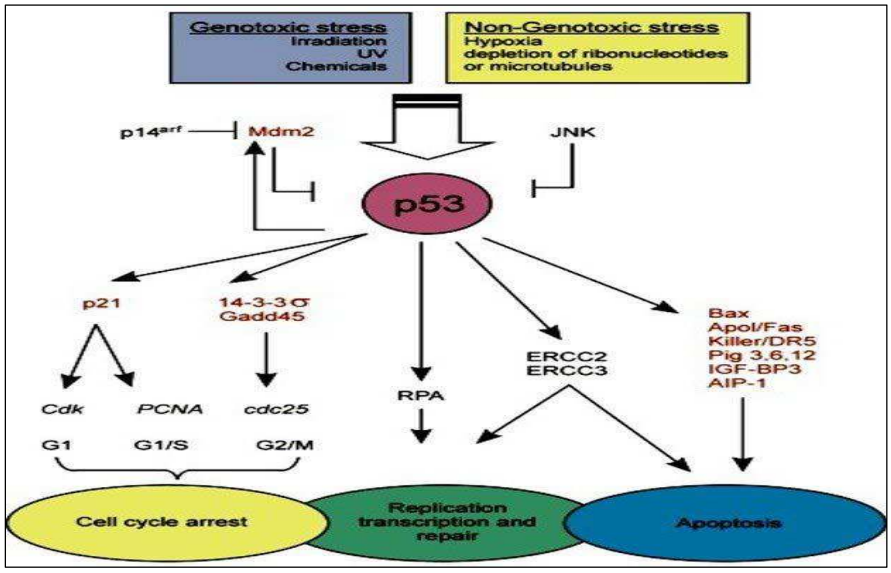

Figure 3: The p53 signaling pathway.[4]

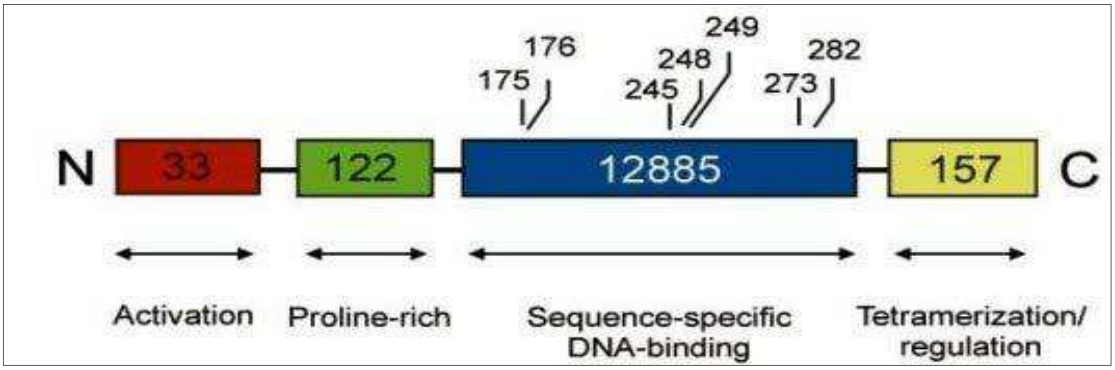

Figure 4: Structure of the p53 protein. [4]

The three most recently changed residues in human cancers are represented using a space-fill model in which each atom is envisioned as a small sphere. The target DNA is outlined to which p53 is bound.

Inactivation of p53 occurs through various mechanisms, including genetic changes (mutation, deletion), with the binding of viral or cellular oncoprotein inactivation of protein is done, and separation in the cytoplasm. The DNA binding domain contains 93% of all mutations identified to date. Since after initial reports that mutations tended to cluster in the central portion of the coding sequence (DNA binding domain) this high frequency may be overestimated, most investigators have limited their analysis to exon 5 to 8. A database of all published inversions is

maintained at the International Agency for Research on Cancer. The most frequently mutated residues are conserved among species and play an important role in the contacts between the protein and target DNA whether direct or indirect. All these mutations result in impaired DNA-binding and loss of transcriptional activity.

Mutations in TP53 are found nearly in every kind of human tumor. In malignancies the mutation prevalence is higher than 50% which includes skin cancer (except melanoma), late stage cancer of bladder, and carcinomas in the aero-digestive tract. Lymphomas and tumors of the prostate, brain, breast, and liver shows an intermediate mutation frequency between (15 to 35%). Leukemia (10%), testicular cancer (< 5%), and malignant melanoma (< 5%) are the kinds of Malignancies with low mutation frequency. In cancers such as breast and colon, TP53 mutations seem to occur late in tumorigenesis. In several other cancers like in the head, neck, lungs and skin, mutations occur very early and may even precede tumor development. The nature and type of inversions is often informative of the mutagenic mechanisms that have caused them, making TP53 an interesting gene to study in molecular epidemiology.

Mutations in the p53 protein can have at least three phenotypic effects: loss of function, in which a missense mutation abrogates p53's ability to block cell division or reverse a transformed phenotype; gain of function (or dominant-positive effect), where mutant p53 acquires novel functions as demonstrated with the introduction of a mutant p53 gene into cells lacking wild-type p53 allele, which induces a tumorigenic phenotype; trans-dominant mutation (dominant-negative effect), seen when a mutant p53 allele is introduced into cells bearing a wtp53 allele, resulting in the ability of mutant p53 to drive wtp53 to a mutant conformation overriding of the normal inhibitory function of p53.

oxidative stress, mutagens—aflatoxins, benzo(a)pyrene, alkylating agents—and inhibitors of topoisomerases. Moreover, damage to the mitotic spindle, ribonucleotide.

p53- dependent Apoptosis

p53 activates the genes transcriptionally and this leads to cell cycle arrest or cell death(apoptosis). p21WAF1/CIP1 is a G1cyclin/cyclin- reliant protein kinase inhibitor and this inhibitor hampers with the activity of a G1cyclin-dependent protein kinase. This results in cell cycle arrest. p53-binding sites in the regulatory region of the gene directly activate transcription of the Bax gene, which is located in mitochondria. When over induced, they induce apoptosis.

There are several potential mediators of p53-induced apoptosis. The bax is a protein which is apoptosis inducing member of the Bcl-2 protein family. p53-binding sites present in the regulatory region of the gene initiates the transcription of the bax gene. Bax is a gene that is located in mitochondria. When there is an over expression of this gene apoptosis is induced.

Gene Therapy using P53

The capacity of wild type P53 to arrest the proliferation of cultured cells and induces apoptosis has raised an enormous interest in the possibility that restoring the p53 function in tumor cells may block tumor development. In addition, the finding that p53 protein is the key factor in determining the response of cancer cells to therapy, has led to the concept that re-introduction of a normal protein may sensitize cells to cytotoxic killing and thus improve therapeutic response. In past ten years, several efforts have been made to translate these laboratory findings into clinical applications. One of the most popular approaches to achieve this goal is gene therapy. Below we summarize the various modalities of p53 based gene therapy that have been described in the recent literature.[5]

Replacement Gene Therapy

The function of TP53 is lost in many cancers through mutation or loss of alleles. Therefore it seems reasonable to try to restore TP53 function by replacing the mutant gene with a functional, wild-type copy. The primary requirement to treat cancer with such replacement gene therapies is the necessity for highly efficient delivery of the wild-type TP53 into tumor cells in vivo. There must also be sufficient expression of functional p53 protein to mediate tumor suppression either through a direct mechanism involving cell death or growth arrest, or by increasing sensitivity to conventional anti-tumor agents. Other critical success factors include a low level of toxicity towards normal cells and the absence of a host immune response against the gene delivery system. The mechanisms of gene delivery can be subdivided in two broad categories: viral and non-viral.[6]

Recent advances in p53 cancer

When a cell suffers from DNA damage by genotoxic, chemotoxic stress or gets abnormal signals from oncogene activation, p53 is activated causing an elevated level of p53 correlated with its two components, acetylation and phosphorylation.

Recent emerging evidence reveals that p53 can also be activated by different physiological and pathological stressors, that includes hypoxia, metabolic stress, ribosomal stress, nutrient deficiency, viral infection, endoplasmic reticulum (ER) stress, and psychological stress.

CONCLUSION

As a crucial sensor of cellular stress, p53 plays a significant role in ensuring proper health and function of all cells by dictating that how processes like apoptosis, Senescence, or transient cell cycle arrest will occur, depending on the level and nature of the stress that the cells encounters as well as to see how severe it is damaged and whether the damage can be reversed. Though severe stress and un-repairable damage results in apoptosis or senescence and modest stress. The repairable damage results in transient cell cycle arrest. Cells will re-enter the cell cycle to produce progeny as soon as the damage in the DNA is repaired.

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