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P53: THE GUARDIAN OF GENOME, APOPTOSIS, AND ITS ROLE IN CARCINOGENESIS

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ABSTRACT
The p53 protein also labeled as tumor protein 53 (or TP53) is one of the best known tumor suppressor protein encoded by the tumor suppressor gene *TP53*, located in the short arm of chromosome 17.(17 P13.1). Since its discovery many studies have looked into its function and its role in cancer. It is not only involved in the induction of apoptosis but is also a key player in cell cycle regulation, development, differentiation, gene amplification, DNA recombination, chromosomal segregation and cellular senescence and so, it is called "the guardian of genome". It is considered as the "ultimate tumour suppressor gene", the function of which is essentially to protect the cell against the occurrence and development of cancers. The term apoptosis is derived from the Greek word meaning "dropping off " and refers to the falling of leaves from tree in Autumn. The biochemical changes seen during apoptosis consist of activation of caspase, DNA and protein breakdown membrane changes and recognition by phagocytic cells. Senescence has already been emerged as an important contributor to TP53 tumor suppressor activity. Another tumor suppressor activity of p53, which is still poorly understood, is its ability to modulate cell migration. The altered cellular movement, loss of p53, increased cell motility contributes to tumor invasiveness. Carcinogenesis is a result of genetic changes in which normal cell are transformed to malignant cell. The mechanism by which evasion occurs is due to disrupted balance of pro-apoptotic and anti-apoptotic proteins, reduced caspase function, impaired death receptor signaling and or senescence. It is well known that p53 acts biochemically as a transcription factor and biologically as a powerful tumor suppressor. It has got a central role in cancer prevention and suppression, and in chemo-sensitization or radio-sensitization.

KEY WORDS: Guardian of Genome, Apoptosis, Senescence, BCL-2, Oncogene, Carcinogenesis.

INTRODUCTION
The p53 protein also labeled as tumor protein 53 (or TP53) is one of the best known tumor suppressor protein encoded by the tumor suppressor gene *TP53*, located in the short arm of chromosome 17.(17 P13.1). The gene is composed of 11 exons, the first of which is non-coding. The product of gene is a 53 Kd nuclear phosphoprotein, composed of 393 amino acids. The functional molecule is a tetramer and acts as a transcription factor. It is involved in cell-cycle check points, apoptosis, genomic stability and DNA repair.[1, 2]

The p53 protein is the sequence specific transcription factor which binds DNA sequences corresponding to repeats of the consensus motif RRRC (A/T) (T/A) Gyyy (where R is a Purine and Y is Pyrimidine). The protein has five structural and functional domains, a proline rich regulatory domain, a sequence specific DNA binding domain, an oligomerization domain, and a c-terminal domain involved in the regulation of DNA binding. In terms of three dimensional structures, the protein is made up of a scaffold of beta-sheets that support flexible loops and helixes which are in direct contact with DNA. The position of these loops and helixes are stabilized by the binding of an atom of zinc. The most frequently mutated portion is sequence specific DNA binding domain. Within this domain several residues are hotspots for mutations.

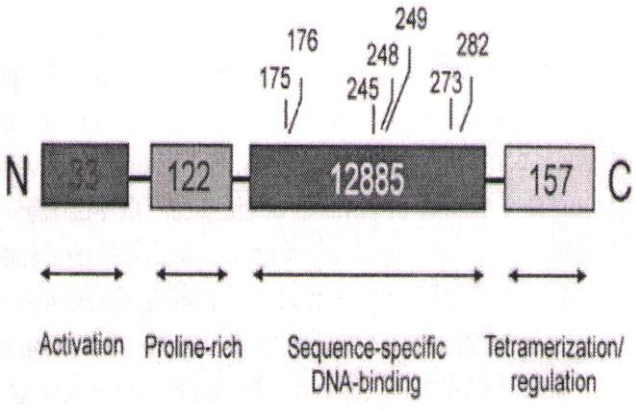

Fig:-1-The guardian of Genome, the p53

THE GUARDIAN OF GENOME

TP53 is a gene and p53 is its product protein. The p53 was first identified in 1979 as transformation related protein and a cellular protein accumulated in the cancer cells, binding tightly to the simian virus 40 (SV40) large T antigens. Initially found to be weakly oncogenic. It was later discovered that the oncogenic property was due to a p53 mutation or what was later called a "gain of oncogenic function".

Since its discovery many studies have looked into its function and its role in cancer. It is not only involved in the induction of apoptosis but is also a key player in cell cycle regulation, development, differentiation, gene amplification, DNA recombination, chromosomal segregation and cellular senescence and so it is called "the guardian of genome".[3, 4]

TP53 is special among cancer genes in at least three aspects i.e.

1. Most of its alterations in cancer are missense mutations. This is uncommon for suppressor genes, which are classically inactivated by deletion or non-sense mutations.

2. It is altered at a significant frequency, between 20 to 80%, in almost every human cancer, irrespective of the organ site or the histological type. This observation stresses the central role of p53 as one of the basic elements of the cellular growth control machinery.

3. The protein itself is essential for many aspects of normal life. This also contrasts with many tumour suppressors which encodes "viral" proteins.

Strikingly the mice deficient in TP53 by homologous recombination show essentially normal development and behaviour. However, when they reach 20 or 30 weeks of age, most of them die from multiple early cancers. Thus, TP53 may be considered as the "ultimate tumour suppressor gene", the function of which is essentially to protect the cell against the occurrence and development of cancers.[5, 6]

In most cells the p53 is almost undetectable because it is rapidly degraded by the proteosome. Upon activation, the protein escapes degradation and accumulates in the nucleus. At the same time it is turned from latent to active form by conformational changes which activate its capacity to transactivate target genes. The main factor controlling p53 accumulation is Mdm2; a protein encoded by a gene which is a target of p53. Mdm2 acts as an ubiquitin ligase to direct p53 out of the nucleus to proteosome, where it is degraded.[7]

APOPTOSIS

The term apoptosis is derived from the Greek word meaning "dropping off " and refers to the falling of leaves from tree in Autumn. Ever since apoptosis was described by Kerr *et al* in 1970, it remains one of the most investigated processes in biological research.[8]

Morphological alterations of apoptotic cell death that concern both the nucleus and cytoplasm are remarkably similar across cell type and species.[9] Morphological hallmark of apoptosis in the nucleus are chromatin condensation and nuclear fragmentation which are accompanied by rounding up of cells, reduction in cellular volume (Pyknosis) and retraction of pseudopodia.[10]

Chromatin condensation starts at the periphery of nuclear membrane, forming a crescent or ring like structure. The chromatin further condenses until it breaks up inside a cell with an intact membrane, a feature described as karyorrhexis.[11]

The plasma membrane is intact throughout the total process. At the later stage of apoptosis some of the morphological features include membrane blebing, ultrastructral modification of cytoplasmic organelles and a loss of membrane integrity. Usually phagocytic cells engulf apoptotic cells before apoptotic bodies occur. This is the reason why apoptosis was discovered very late in the history of cell biology in 1972, and when, apoptotic bodies are seen *in vitro* under special conditions. The biochemical changes seen during apoptosis consist of activation of caspase, DNA and protein breakdown membrane changes and recognition by phagocytic cells.[12]

Caspase are central to the mechanism of apoptosis as they are both initiator and executioners. They are activated by intrinsic (or mitochondrial) and extrinsic (or death receptors) pathways of apoptosis. Both pathways eventually lead to a common pathway or execution phase of apoptosis. A third less well known initiation pathway is the intrinsic endoplasmic reticulum pathway.[13]

Senescence: Senescence has already been emerged as an important contributor to TP53 tumor suppressor activity. It is an important biological consequence of p53 activation by genotoxic stress. Cellular senescence refers to the essentially irreversible arrest of cell proliferation (growth). It is established and maintained by at least two major tumor suppressor pathways- the p53/p31 and p16NK4a/pRB pathways, and is now recognized as a formidable barrier to malignant tumorogenesis. [14]

Cell migration

Another tumor suppressor activity of p53 which is still poorly understood is its ability to modulate cell migration. Roax and co- workers have shown that p53 inhibits Cdc-42 induced philopodia formation.[15]

Absence of p53 in mouse embryonic fibroblast induced rounded blabbing movements through over action of RhoA and Rock-dependent translocation of RhoA to membrane blebing structure.[16]

Thus by altering cellular movements, loss of p53, (as well as the expression of one of the p53 isomers, Δ133p53β) increased cell motility and may thus contribute to tumor invasiveness.

APOPTOSIS AND CARCINOGENESIS

Carcinogenesis is a result of genetic changes in which normal cell are transformed to malignant cell. Apoptosis is a mechanism of cell death. Reduced apoptosis plays a vital role in carcinogenesis.[17] The mechanism by which evasion occurs can be broadly divided as fallows; -[Fig-2].

1. Disrupted balance of pro-apoptotic and anti-apoptotic proteins.
2. Reduced caspase function.
3. Impaired death receptor signaling.
4. Senescence.

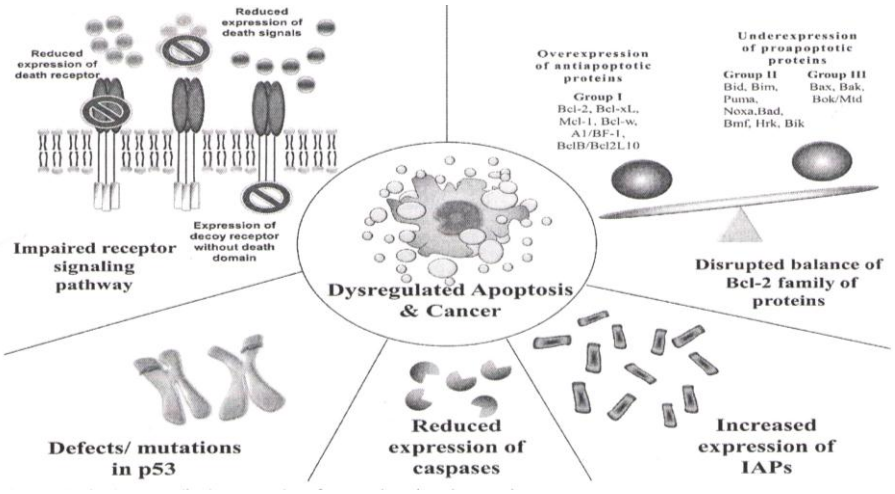

Fig:-2-The mechanisms of Carcinogenesis.

THE DYSREGULATED APOPTOSIS AND CANCER

1. Disrupted balance between pro and anti-apoptotic proteins: Many proteins have been reported to exert pro or anti apoptotic activity in the cell. It is not the absolute quantity but rather the ratio of these pro and anti-apoptotic proteins that plays an important role in the regulation of cell death. Besides over and under expression of certain genes (hence the resultant regulatory proteins) have been found to contribute to carcinogenesis by reducing apoptosis in the cancer cells.

1.1. The BCL-2 family of proteins

The BCL-2 family of proteins is composed of pro-apoptotic and anti-apoptotic proteins that play a pivotal role in the regulation of apoptosis, especially via the intrinsic pathway as they reside upstream of irreversible cellular damage and act mainly at the mitochondria level.[18]

When there is disruption in the balance of anti-apoptotic and pro-apoptotic members of Bcl-2 family, the result is dysregulated apoptosis in the affected cells. This can be due to over expression of one or more anti-apoptotic proteins or under expression of one or more pro-apoptotic proteins or a combination of both.

Example-1- Over-expression of Bcl-2 protected prostate cancer cells from apoptosis.[19]

Example-2- In colorectal cancers with microsatellite instability, mutations in the *bax gene* are very common. Miquel *et al* demonstrated that impaired apoptosis resulting from *bax* (G) 8 frame shift mutations could contribute to resistance of colorectal cancer cells to anti cancer treatment.[20]

2. The p53- Defects/mutations

P53 is the most interesting target for the cancer biologist due to its central role in carcinogenesis. It was first discovered in 1979 as oncogene, [21] and rediscovered as tumor suppressor gene in 1989.[22]

It is well known that p53 acts biochemically as a transcription factor and biologically as a powerful tumor suppressor. Given the central role of p53 in cancer prevention and suppression and in chemo-sensitization or radio-sensitization, p53 has to be abrogated during carcinogenesis for most cancer to arise. Indeed p53 is inactivated by point mutation in more than 50% of human cancers with a majority of mutation occurring in the DNA binding domain, which either changes wild p53 conformation (confirmation mutants e.g. 175H,2495,281G) or abolish its DNA contact(contact mutants e.g. 248W, 273H).[23]

Furthermore, in cancer carrying a wild p53, often malfunction, as a result of either being degraded by over expressed Mdm2 [4] or being excluded from the nucleus where p53 acts as a transcriptional factor.[24, 25, 26]

The p53 protein, also called tumor protein 53 (or TP 53) is one of the best known tumor suppressor proteins encoded by the tumor suppressor gene *TP53* located in the short arm of chromosome 17 (17p13.1) it is named after its molecular weight i.e. 53 Kda.[27] Defects in the p53 tumor suppressor gene have been linked to more than 50% of human cancers.

Various types of genotoxic and non genotoxic stresses can lead to p53 activation like

- Genotoxic damage causing telomerase erosion.
- Hypoxia.
- Nutritional starvation
- Mitochondrial biogenesis stresses.
- Ribosomal biogenesis.
- Spindle poisoning.
- Heat or cold shock.
- Protein unfolding problems.
- Oncogenic activation.[28]

Damage to the mitotic spindle, ribonucleotide depletion, hypoxia, heat shock and exposure to nitric oxide can also induce p53. Induction follows a different time-course, depending upon the nature and intensity of stress. Induction in response to stress is a multi step phenomena. It involves phosphorylation of p53 in the N-terminus. e.g. by kinase activated after DNA damage such as ATM or chk-2 and dissociation of p53-Mdm-2 interaction. Other changes in protein includes: acetylation of the c-terminus, (by acetyl-transferases of CBP/p300 family).[29]

- Conformational changes in the C-terminus, leading to the unmasking of the DNA- binding domain, and, changes in oxidation-reduction in the DNA-binding domain. All these changes turn the protein into an active form which binds DNA with high affinity.

The mechanism underlying p53 selectivity towards target genes have been studied by several investigators in recent years. Resnick and coworkers.[30] showed that the, transactivation (TA) capacity of p53 towards different target genes, was greatly influenced by the overall structure of the p53 response element (RE) [31] in addition to its primary sequence and by the, level of p53 protein expression. Notably the number of spacer nucleotides separating the two palindrome sequences that constitute a consensus p53-RE greatly impacted on DNA binding. Increasing the size of this spacer reduced binding efficacy. A novel functional motif containing a p53-RE half-site and an estrogen receptor RE has been identified, in the VEGFR1/FLT1 gene promoter at a polymorphic site (C/T).[32]

This site confers responsiveness to both p53 and estrogens. In carriers of t allele, VEGF-r/flt-1 is under the control of both p53 and estrogen receptors and VEGF-R expression is strongly activated in presence of both factors. Although the occurrence of such motifs in the entire genome and their functional impact remains to be determined, these examples show that the p53 regulatory network may be more complex than expected from canonical p53-RE. Furthermore p53 half sites can also be recognized by some p53 mutants, a feature that may expand their biological effects.[33] Once activated p53 can trigger several cellular events via two distinct and parallel pathways, transcription dependent and transcription independent.

Examples of the transcription independent pathways include binding of p53 to components of the DNA replication/repair machinery such as the helicases ERCC2 and ERCC3 or the replication protein RPA. Genes transcriptionally regulated by p53 includes cell cycle regulators in G1 and in G2 phase (p21/waf-1, 14-3-3s, GADD45), regulators of apoptosis (Bax, CD 95/ FAS, KILLERS/DR5,p53 AIP1,PIG3,IGE-BP3) and genes involved in cellular response to stress such as inducible forms of nitric oxide synthesis(NoS2) and cyclooxygenase (COX-2) which are both repressed by p53. How p53 selects from the set of alternative response (e.g. choosing in between cell cycle arrest or apoptosis) depends upon the nature and the amplitude of the inducing signal as well as the cell and tissue type.

P53 activation provokes cellular blockage in G1 and G2/M which are the check-points of cellular cycle. A crucial role for the induction of the G1 cellular blockage plays p21 transcriptional activation. P21 binds and inhibits the activity of the cyclin-CDK complexes that leads to increased expression of the phosphorylated (Active) form of pRb and of a subsequent G1 cellular blockage. P53 takes part in the induction of cellular blockage during the G2 phase. P53 causes decreased transcriptional regulation of cyclin B as well as cellular blockage at the margin of the G2/M phase. Cyclin b is a major regulator required during the mitosis. GADD-45 and 14-3-3 are other transcriptionally activated proteins taking part in the induction of cellular blockage in the G2 point of the cellular cycle. P21 and GADD-45 affects the activity of PCNA that takes part in the process of DNA repair.[34]

CONCLUSION

The p53 and its action (apoptosis) has become an interesting molecule for biologists, oncologist and a plethora of scientists. Its pathways, actions, are being explored to understand the mechanism of carcinogenesis as well as to develop strategies to counter it. Keeping in mind p53 and its action, few of the recent developments in the direction of onco-therapeutics are outlined below.

1. Targeting the Bcl-2 family of proteins.[35]
2. Silencing the Bcl family anti-apoptotic proteins/genes.[36]
3. p53 based gene therapy.[37]
4. p53 based drug therapy.[38]
5. p53 based immunotherapy.[39]
6. Targeting IAPs and XIAPS.[40]
7. Targeting surviving.[41, 42]

8. Other IAP antagonists.[43]
9. Targeting caspase and caspase based drug therapy.[44]
10. Caspase based gene therapy.[45]

There is abundance of data available to the various aspects of p53.the major concern is whether these treatment strategies induce resistance in tumour and whether they will cause normal cell to die in massive numbers remains unanswered. This is a true concern because conventional anticancer drugs wipe out both normal and cancer cells with brutal side effects. So a lot has to be done to find out the targeted therapy without harm to normal cells .Yet another field to explore is to prevent cancer from occurring rather than treating them after its occurrence. The answer probably will be found out in futuristic research.

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