



REVIEW OF p53

Dr. Prashant Rao¹, Dr. V. V. Kulkarni², Dr. Mayur Choudhary¹, Dr. Prasad Karande³ and Dr. Shrikant Sonune*⁴

¹Associate Professor, Bharati Vidyapeeth Deemed to be University Dental College and Hospital, Pune.

²Professor, Bharati Vidyapeeth Deemed to be University Dental College and Hospital, Pune.

³Associate Professor. D. Y. Patil Dental College and Hospital, Charoli, Lohegaon, Pune.

⁴Dental Surgeon, SDH Karmala.

***Corresponding Author: Dr. Shrikant Sonune**

Dental Surgeon, SDH Karmala.

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ABSTRACT

The tumor suppressor gene, p53, is the most commonly mutated gene in human cancers. P53 an open reading frame of 393 amino acids, the p53 gene has 11 exons with several conserved domain. Under normal circumstances, p53 protein is present in the cell at extremely low levels with the protein being relatively inactive and inefficient at binding target DNA. Various types of stress increase p53 protein levels in the cell and these include DNA damage, heat shock, hypoxia, hyperoxia, cytokines, growth factors, metabolic changes, oncogenes. This subsequently results in adaptive cum protective responses. Loss of normal p53 function is potentially harmful when cells with damaged DNA are left unchecked and permitted to continue replicating. This review emphasize various aspects of P53.

KEYWORDS: Mutations, Oncogenesis, p53.

INTRODUCTION

The tumor suppressor gene, p53, is the most commonly mutated gene in human cancers. over 10,000 mutations have been recorded and p53 mutations are present in about 40% of human cancers.^[1,2] It is located on chromosome 17p 13, the gene, it encodes a 53 kilodalton nucleophosphoprotein which serves as a transcription factor with a pivotal role in regulation of the cell cycle. P53First identified in 1979, p53 was initially thought to be another of an array of oncogene product.^[3,4] later p53 found to be tumour-suppressing rather than tumor inducing.^[5] In-depth research into the field has resulted in a plethora of publications with p53 earning the distinction of being selected as "molecule of the year" by "Science" in 1993. This review aims to highlight the facts about p53.

p53 Protein: P53 an open reading frame of 393 amino acids, the p53 gene has 11 exons with several conserved domain^[6] A sequence-specific DNA binding domain spans the centre at amino acid positions 100-300. Encoded by exons 5-8. Binding to DNA is optimized when four p53 molecules interact with target DNA. This tetramerisation of the p53 protein is controlled by the tetramerisation domain which is another conserved domain next to the sequence-specific DNA-binding domain.^[7] The basic C-terminal most likely influences sequence-specific DNA binding.^[8] The acidic N-terminal

helps in expression of target genes following sequence-specific DNA binding to target genes and is also important for maintaining the stability of the p53 molecule through its interaction with Mdm2 protein.^[9] Adjacent to the N-terminal, lies a region that binds signal transduction molecules carrying SH3.^[10]

Functional Aspects of p53

Regulation of p53

Under normal circumstances, p53 protein is present in the cell at extremely low levels with the protein being relatively inactive and inefficient at binding target DNA.^[11] This is mainly due to its interaction with Mdm2 protein. The Mdm2 oncogene was first amplified from a double minute chromosome in a derivative of tumourigenic mouse 3T3 cells.^[12] The human homologue, Hdm2, has also been found amplified in 30-40% of human sarcomas.^[13] Mdm2 protein interacts with p53 protein at its N-terminus and regulates p53. The interaction of the two proteins inhibits the ability of p53 to activate transcription of downstream gene.

Effects of stress on p53 protein: Various types of stress increase p53 protein levels in the cell and these include DNA damage, heat shock, hypoxia, hyperoxia, cytokines, growth factors, metabolic changes, oncogenes etc.^[6] p53 induced response to cellular stress can be either in the form of arrest of growth or apoptosis of the

cell. Both arrest of growth of cell and apoptosis both responses can be seen as adaptive for the cell i.e. the cell is either allowed time for repair through a process of cell cycle arrest or undergoes ablation and dies when somehow the insult is viewed as irreparable. p53 arrests the damaged cells mainly at 2 cell cycle checkpoints, G1 or G2.

G1 arrest^[14]: Under normal circumstances, exit from G1 and entry into the S phase requires phosphorylation of pRb (retinoblastoma protein) by G1-specific cyclin cdk complexes. This releases E2F, a transcription factor which is bound to hypophosphorylated pRb and which is required for entry into the S phase. In the presence of damaged DNA there is an increase of wild type p53. Such wild type of p53 inhibits progress to S phase.

G2 arrest^[15]: Although earlier studies on p53 induced cell cycle arrest focused mainly on G1 arrest, it has become increasingly evident that p53 protein can also lead to arrest at G2 of the cell cycle. The cyclin B1/Cdc2 complex appears to be the major regulatory factor required for entry into the M phase of the cell cycle. p53 is known to induce Gadd45 protein which inhibits activity of cyclin B1/Cdc2 complex. With this disruption of cyclin B1/Cdc2, cells are prevented from entry to the mitotic phase.

Apoptosis^[16,17]: p53 induced genes associated with apoptosis of the damaged cell are being increasingly recognised but the best known so far is Bax. Under certain conditions of cellular damage p53 induces expression of Bax, a member of the Bcl-2 family and this leads to cell Apoptosis. Besides Bax, other downstream genes activated by p53 and which are involved in the apoptotic process have been identified and these include PAG608 and Fas/Apo-1.

p53 in Oncogenesis: Under normal circumstances, cells respond to stress by increasing p53 level. This subsequently results in adaptive cum protective responses. The cell is thus provided increased time to repair damage to the cellular DNA or undergoes apoptosis if the damaged DNA is not to be repaired. It is thus conceivable that loss of normal p53 function is potentially harmful when cells with damaged DNA are left unchecked and permitted to continue replicating.

Loss of p53 function can arise from several causes but the most common is still that due to mutation in the p53 gene. Majority of the mutations lead to inactivation of the normal protective p53 function. Among the mutational changes, about 85% are missense and of these about 95% lie within the sequence-specific DNA binding domain i.e. exons 5-8.^[19] Deletions and insertions of the gene also occur but are less frequent. Besides mutations, infection by high risk human papillomavirus (HPV) has a unique mechanism for inactivating p53 protein. E6 protein of high-risk HPV binds p53 protein and promotes degradation of p53 via the ubiquitin pathway.^[20]

This leads to loss of wild type p53 protein and abrogation of normal p53 function. The amplification of Mdm2 gene in some human sarcomas with the consequent overexpression of Mdm2 protein naturally targets p53 protein for increased ubiquitination.

Most p53 mutations are sporadic and acquired in somatic cells. Nevertheless, in the Li-Fraumeni syndrome, a mutant p53 allele is inherited with cancers occurring on a second hit mutation.^[85] With an approximately 25 times increased risk of developing malignancy patients with Li-Fraumeni syndrome often develop multiple tumours at a younger age. A multitude of cancers have been associated with inactivation of p53 and include sarcomas e.g. osteosarcoma, rhabdomyosarcoma, glioblastoma multiforme, anaplastic astrocytoma, malignant ependymoma, leukaemias, lymphomas and carcinomas of colorectal, breast, lung, liver, oesophageal, bladder, skin and cervical origin.

Major Impacts on Cancer Management

Among the Various aspects of p53 advances, probably the most meaningful would lie in tumour therapy. The more promising so far includes the induction of tumour regression following injection of wild type p53 into human lung carcinoma.^[22]

Recent Developments

Research in the p53 area is continuing at a rapid pace and understanding of this very important cell-cycle regulator is increasing all the time with new discoveries. For example, once believed that mutations of the p53 gene mainly led to loss of function of p53 protein, some workers have recently shown that some mutations can give rise to new functions or commonly referred to as "gain of function mutants".^[23]

Another new function of p53 in tumorigenesis seems to be emerging with the discovery that wild type p53 protein normally stimulates production of endogenous thrombospondin-1 (TSP-1), a potent inhibitor of angiogenesis.^[24] The switch to the malignant phenotype in cultured fibroblasts from patients with Li-Fraumeni syndrome seems to be accompanied by loss of wild-type p53 protein and downregulation of TSP-1. Hence, it appears that in malignancy, loss of p53 function may be important for the switch to the angiogenic phenotype which encourages growth of the tumour.

Dosage effects of p53 protein in the production of tumours are also being investigated. Although it may be expected that obliteration of both alleles of p53 is necessary for development of cancers, this being in line with the Knudson's with neoplastic change. This sublimates the theory that the level of p53 protein is important for cellular protection and loss of one p53 allele has a potentially increased risk of neoplastic transformation.^[25]

Homologues of p53 are also being described although it was originally thought that p53, unlike many other cell regulators, did not belong to a superfamily. Of the human p53 homologues, p63 and p73 have been better studied but their actual functions still require further clarification.^[26]

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