IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, February 2023
Impact Factor: 7.301

T53: A Mystery Gene

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Abstract: *T53 A regulatory protein which controls the cell division also it acts as tumour suppresser. That means it controls the cell division to avoid the uncontrolled division of cell to resist the growth of tumour . it is located in the nucleolus of the cell throughout the body here it is directly attached to the DNA . when the DNA gets damaged by some of the reasons this gene plays an crucial role , it repairs the damaged DNA or the cell will go under apoptosis . if the DNA can be repaired the he p53 activates the other proteins to fix damage . if the damage can't be reversed it prevents the DNA replication and cell from dividing to prevent formation of tumour.*

Keywords: T53**,** regulatory protein, Mutant p53 in cancer progression and targeted therapies, P53 Role in Disease, Function of p53, Human TP53 gene, regulatory protein

I. INTRODUCTION

T53 A regulatory protein which controls the cell division also it acts as tumour suppresser. That means it controls the cell division to avoid the uncontrolled division of cell to resist the growth of tumour . it is located in the nucleolus of the cell throughout the body here it is directly attached to the DNA . when the DNA gets damaged by some of the reasons this gene plays an crucial role , it repairs the damaged DNA or the cell will go under apoptosis . if the DNA can be repaired the he p53 activates the other proteins to fix damage . if the damage can't be reversed it prevents the DNA replication and cell from dividing to prevent formation of tumour.

Because of its function and crucial role in DNA repair it is also called as the guardian gene. This article is focused on the function of p53 genome and its role.

1.1 What is P53

A regulatory protein called p53 that is often mutated in human malignancies is also known as tumour protein P53, cellular tumour antigen p53 (UniProt name), or transformation-related protein 53 (TRP53). The p53 proteins, which were once believed to be a single protein and are sometimes referred to as such, are essential in vertebrates because they inhibit the development of cancer. As a result of its function in preserving stability by guarding against genome mutation, p53 has been referred to as "the guardian of the genome." TP53 is therefore categorized as a tumour suppressor gene. (1)

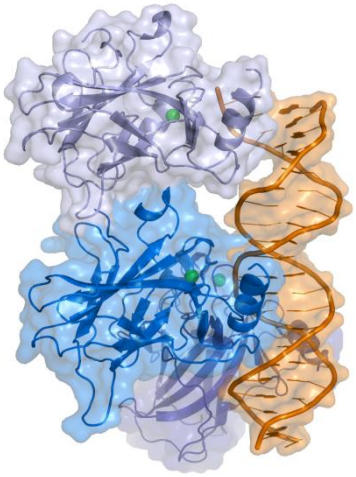

Image: TP53

Source: Wikipedia.org/p53

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The most often mutated gene (>50%) in human cancer is the TP53 gene, which suggests that the TP53 gene is essential for avoiding the development of cancer. The TP53 gene produces proteins that bind to DNA and control gene expression to stop genome mutations. The human TP53 gene encodes not just the full-length protein but also at least 15 different protein isoforms.

The TP53 gene is found on the short arm of chromosome 17 in humans (17p13.1). The 20 kb long gene, which overlaps the Hp53int1 gene, has a non-coding exon 1 and an extremely lengthy first intron of 10 kb. However, the sequences identified in invertebrates only distantly resemble those of mammalian TP53. The coding sequence comprises five areas that have a high degree of conservation in vertebrates, namely in exons 2, 5, 6, 7 and 8. In the majority of mammals for whom whole genomic data are available, TP53 orthologs have been found.(2)

1.2 Human TP53 Gene

At codon position 72 of exon 4 in humans, a frequent polymorphism includes the exchange of an arginine for a proline. Numerous research have looked at whether this polymorphism and cancer risk are related genetically, although the findings have generated some debate. For instance, a 2009 meta-analysis that looked for a relationship for cervical cancer came up empty. A 2011 study discovered that the TP53 proline mutation did have a significant impact on men' likelihood of developing pancreatic cancer. Proline homozygosity at TP53 codon 72 was linked to a lower incidence of breast cancer, according to a study of Arab women.

According to one study, TP53 codon 72 polymorphisms, MDM2 SNP309, and A2164G may all be linked to an increased risk of developing non-oropharyngeal cancer, and MDM2 SNP309 combined with TP53 codon 72 may hasten this process in females. According to a 2011 study, TP53 codon 72 polymorphism is linked to a higher risk of developing lung cancer.

2011 meta-analyses revealed no conclusive relationships between TP53 codon 72 polymorphisms and the risk of colorectal or endometrial cancer. An link between those without a family history of cancer and those with non-mutant arginine TP53 was discovered in a 2011 research of a Brazilian birth cohort. The p53 homozygous (Pro/Pro) genotype was linked to a considerably higher risk of renal cell carcinoma, according to a 2011 research.

1.3 Function of p53

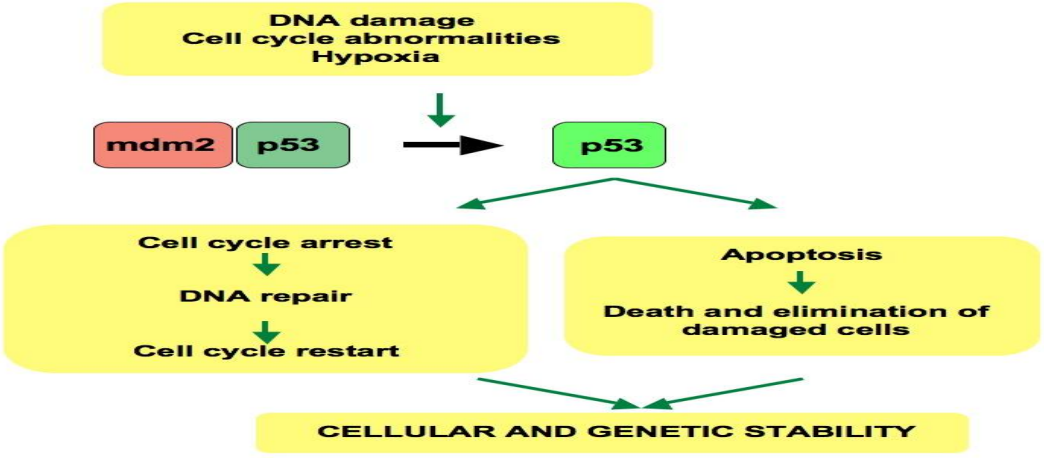

Image: TP53

Source: Wikipedia.org/p53

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1.4 DNA Damage and Repair

Through a variety of ways, p53 affects the control of the cell cycle, apoptosis, and genomic stability. When DNA is damaged, it can cause DNA repair proteins to be activated. Consequently, it could play a significant role in ageing. By keeping the cell cycle at the G1/S regulation point after detecting DNA damage, it can stop the growth of an organism. If it keeps the cell here for a long enough period of time, the DNA repair proteins will have time to repair the damage before the cell can move on to the next phase of the cell cycle. If the DNA damage is found to be irreversible, it might start apoptosis, or programmed cell death. Senescence's reaction to short telomeres depends on it.

p21 and a large number of additional downstream genes are encoded by WAF1/CIP1. The G1-S/CDK (CDK4/CDK6, CDK2, and CDK1) complexes, which are crucial for the G1/S transition in the cell cycle, bind to p21 (WAF1), preventing them from functioning.

The cell is unable to advance to the following stage of cell division when p21(WAF1) complexes with CDK2. The p21 protein, which serves as the "stop signal" for cell division, will not be present due to a mutant p53's inability to bind DNA effectively. Studies on human embryonic stem cells (hESCs) frequently discuss the G1/S checkpoint pathway's nonfunctional p53-p21 axis and its implications for cell cycle control and the DNA damage response (DDR). It is significant to note that whereas p21 protein cannot be seen in hESCs after the DDR, p21 mRNA is unquestionably present and increased. Numerous microRNAs, including miR-302a, miR-302b, miR-302c, and miR-302d, are activated by p53 in this cell type and subsequently prevent p21 from being expressed in hESCs.

In order to stop the cell cycle and enable repair, the p21 protein binds directly to the cyclin-CDK complexes that advance the cell cycle and suppresses their kinase activity. Additionally, differentiation-related growth arrest and a longer-lasting growth arrest related to cellular senescence can both be mediated by p21. Numerous p53 response elements found in the p21 gene facilitate direct binding of the p53 protein and transcriptional activation of the p21 gene. Because p14ARF connects the p53 and RB1 pathways, it is possible that they might control one another.UV radiation, which also damages DNA, can increase p53 expression. In this situation, p53 might start the processes that result in tanning.(3,4)

1.5 Stem Cells

P53 levels are crucial for maintaining stem cells throughout development and the remainder of a person's life. P53 levels in human embryonic stem cells (hESCs) are kept at a minimum and are inactive. This is due to the fact that p53 activation causes hESCs to rapidly differentiate.

Studies have demonstrated that p53 promotes differentiation of hESCs and plays a crucial function in the cell cycle as a differentiation regulator by demonstrating that knocking down p53 slows differentiation and that adding p53 increases spontaneous differentiation. In hESCs, when p53 is activated and maintained, it raises p21 to provide a prolonged G1. Usually, this results in the elimination of S-phase entrance, which halts the cell cycle in G1 and promotes differentiation. However, research in mouse embryonic stem cells has recently demonstrated that P53 expression does not always result in differentiation. Additionally, miR-34a and miR-145 are activated by p53, which subsequently inhibit the hESCs pluripotency factors and promote differentiation.

P53 regulation in adult stem cells is crucial for maintaining stemness in adult stem cell habitats. The hypoxia inducible factors HIF-1 and HIF-2 influence the levels of p53 in these niche cells in response to mechanical cues like hypoxia. HIF-2 inhibits p53 whereas HIF-1 stabilises it. Induced pluripotent stem cells, cancer stem cell phenotype, and other stem cell functions and behaviours, such blastema development, are all significantly impacted by p53 suppression. It has been demonstrated that cells with lower p53 levels may convert into stem cells considerably more effectively than healthy cells. According to several studies, the absence of cell cycle arrest and death increases the possibility of reprogramming in cells. Additionally, it has been demonstrated that a key factor in salamander blastema development in the legs is decreased levels of p53. In order to operate as a barrier between stem cells and a differentiated stem cell state, as well as a barrier between functioning stem cells and malignant stem cells, p53 regulation is crucial.

P53 also has tissue-level anticancer effects that function by preventing angiogenesis in addition to the cellular and molecular effects mentioned above. As tumours expand, new blood vessels must be recruited to supply them. P53 prevents this by

1. interfering with tumour hypoxia regulators HIF1 and HIF2,

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2. preventing the production of angiogenic promoting factors, and
3. directly increasing the production of angiogenesis inhibitors like arresten.

It has been demonstrated that p53 promotes implantation in mouse reproduction and perhaps human reproduction through controlling Leukemia Inhibitory Factor.(5,6)

1.6 Regulation

A cellular stress sensor, p53 plays this role. It is often flagged for destruction by the E3 ubiquitin ligase protein MDM2, which allows it to be preserved at low levels in most cases. Numerous stimuli, including as oxidative stress, DNA damage brought on by UV, IR, or chemical agents like hydrogen peroxide, trigger the activation of the p53 gene. ribonucleotide depletion, osmotic stress, and aberrant oncogene expression. Two significant occurrences characterize this activation. First, a significant increase in the p53 protein's half-life causes a rapid accumulation of p53 in stressed cells. Second, p53 is compelled to become active in these cells as a transcription regulator via a conformational shift. The crucial process that causes p53 to become active is the phosphorylation of its N-terminal domain. With its many phosphorylation sites, the N-terminal transcriptional activation domain might be thought of as the protein kinases' principal target when transmitting stress signals

One can broadly split the protein kinases that are known to target this transcriptional activation region of p53 into two categories. The MAPK family of protein kinases, which includes the JNK1-3, ERK1-2, and p38 MAPK members, is known to react to a variety of stresses, including membrane disruption, oxidative stress, osmotic shock, thermal shock, and others. The genome integrity checkpoint, a molecular cascade that detects and reacts to various kinds of DNA damage brought on by genotoxic stress, is thought to involve a second set of protein kinases (ATR, ATM, CHK1 and CHK2, DNA-PK, CAK, TP53RK). Additionally, oncogenes promote p53 activation through the protein p14ARF.

Through constant p53 degradation, p53 levels are kept low in cells that are not under stress. Mdm2 (also known as HDM2 in humans) is a protein that attaches to p53, stops it from working, and moves it from the nucleus to the cytoplasm. Additionally, Mdm2 functions as a ubiquitin ligase, attaching ubiquitin covalently to p53 and designating p53 for destruction by the proteasome. The ubiquitylation of p53 can be reversed, though. Mdm2 is likewise activated upon p53 activation, creating a feedback loop. When certain pressures are present, p53 levels can oscillate or produce repeated pulses, and these pulses may be crucial in deciding whether the cells survive the stress or not.

In circumstances where p53 activity has been suppressed, MI-63 binds to MDM2, reactivating p53. USP7 (or HAUSP), a ubiquitin-specific protease, may remove ubiquitin from p53, shielding it from proteasome-dependent destruction by using the ubiquitin ligase route. One way that p53 is stabilised in response to oncogenic shocks is in this way. Additionally, it has been demonstrated that USP42 deubiquitinates p53 and may be necessary for p53's capacity to react to stress.

HAUSP is mostly present in the nucleus, while some of it can also be detected in the cytoplasm and mitochondria, according to recent studies. P53 becomes stabilised as a result of HAUSP overexpression. Because HAUSP binds to and deubiquitinates Mdm2, p53 levels are not reduced when HAUSP levels are reduced instead, p53 levels are increased. In unstressed cells, it has been demonstrated that HAUSP is a more effective binding partner for Mdm2 than p53.

However, it has been discovered that USP10 is present in the cytoplasm of cells that are not under stress and deubiquitinates cytoplasmic p53 to reverse Mdm2 ubiquitination. USP10 translocates to the nucleus after DNA damage and helps keep p53 stable. Additionally, Mdm2 and USP10 do not interact.

The aforementioned protein kinases interfere with Mdm2-binding by phosphorylating the N-terminal end of p53. The recruitment of other proteins, such as Pin1, causes p53 to shift shape, further preventing Mdm2-binding. Additionally, phosphorylation enables the attachment of transcriptional coactivators like as p300 and PCAF, which acetylate the carboxy-terminal end of p53 to reveal its DNA binding domain and enable it to activate or repress particular genes. Sirt1 and Sirt7 are two deacetylase enzymes that may deacetylate p53, which prevents apoptosis from occurring. Additionally, some oncogenes can promote the transcription of proteins that bind to MDM2 and stop it from functioning.

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1.7 P53 Role in Disease

Tumor suppression is greatly hampered by TP53 gene damage. People with Li-Fraumeni syndrome, a condition in which only one functioning copy of the TP53 gene is inherited, are more prone to develop malignancies in early adulthood.

Mutagens (chemicals, radiation, or viruses) can also alter the TP53 gene, which raises the risk of uncontrolled cell division. The TP53 gene is mutated or deleted in more than 50% of human malignancies. Genomic instability brought on by p53 loss frequently manifests as the aneuploidy phenotype.

Increasing p53 levels may appear to be a therapy for tumours or a way to stop them from spreading. But because it can speed up ageing, this is not a useful therapy strategy. Some hope exists in reestablishing endogenous normal p53 function. According to research, this repair can cause some cancer cells to shrink without harming healthy ones. The methods through which tumour regression takes place essentially depend on the kind of tumour. For instance, restoring endogenous p53 activity in lymphomas may cause apoptosis while restoring normal cell proliferation. As a result, pharmacological reactivation of p53 is presented as a potential cancer therapeutic strategy. In 2003, China authorised Gendicine, the first commercial gene therapy, for the treatment of head and neck squamous cell carcinoma. It utilises a modified adenovirus to deliver a functional copy of the p53 gene.(7)

The TP53 gene's expression of the p53 protein can be impacted by certain infections. One such instance is the human papillomavirus (HPV), which produces the protein E6 that binds to and deactivates the p53 protein. Repeated cell division is made possible by this process, which works in conjunction with the HPV protein E7's inactivation of the cell cycle regulator pRb to cause warts. A benign wart may develop into low or high-grade cervical dysplasia, which are reversible forms of precancerous lesions, as a result of some HPV strains, particularly types 16 and 18. Chronic cervix infection over time can result in permanent alterations that eventually lead to carcinoma in situ and invasive cervical cancer. This is a result of HPV genes, especially those that code for E6 and E7, the viral oncoproteins that are preferentially maintained and produced in cervical malignancies as a result of the integration of viral DNA into the host genome.(8)

In the cells of healthy individuals, the p53 protein is continuously generated and destroyed, causing damped oscillation (see a stochastic model of this process in). MDM2 binding is related to the p53 protein's destruction. The p53 protein triggers MDM2, which then induces itself in a negative feedback loop. Mutant p53 proteins frequently do not stimulate MDM2, which results in very high quantities of p53 building up. Additionally, normal p53 protein levels can be inhibited by the mutant p53 protein itself. Single missense mutations in p53 have been proven to impair p53 stability and function in specific circumstances. It has been demonstrated that suppressing p53 in human breast cancer cells increases the expression of the CXCR5 chemokine receptor gene and activates cell migration in response to the chemokine CXCL13.(9)

According to one study, the survival of Chronic Myeloid Leukaemia (CML) cells depended on the proteins p53 and Myc. Drugs that target the p53 and Myc proteins produced beneficial effects in CML-affected animals.(9)

1.8 Mutent p53 in cancer progression and targeted therapies

The tumour suppressor gene with the highest frequency of mutations in human cancer is TP53. The bulk of p53 mutations are missense mutations, which result in the production of fully mutated p53 proteins. Mutant p53 (Mutp53) proteins typically develop oncogenic gain-of-functions (GOF) that stimulate carcinogenesis in addition to losing wild-type p53-dependent tumour suppressive abilities. the most current developments in our knowledge of mutp53's oncogenic GOF and possible mutp53-targeting treatments for human malignancies. Promising medications that are presently undergoing clinical trials as well as cutting-edge treatment approaches, such as immunotherapies that specifically eradicate mutp53-expressing tumour cells and CRISPR/Cas9-based genome editing of mutant TP53 alleles, are of special importance.(10,11)

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