

## **P53 Tumor Suppressor Gene and Cancer**

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### **Abstract**

Human cells face many dangers, including chemicals, viruses and ionizing radiation. If cells are damaged in sensitive places by these attackers the effect can be disastrous. Highly regulated processes become deregulated due to genetic alterations that lead to cellular transformation. Guardians of genomes (Tumour suppressor genes) play a crucial role in the protection of our cells. Tumour suppressor genes are involved in a diversity of cellular processes such as cell cycle control, replication, recombination, signal transduction, repair, differentiation and aging. One of our guardian genes is p53 Tumour suppressor gene; restrict cell cycle progression, p53 lost its function by genetic alteration (mutation) or some external factors. TP53 gene contribute to about half of the cases of human cancer. Most of the mutations that cause mutant p53 protein production are missense mutations, mutant p53 unable to stop multiplication in the damaged cell. The function of p53 protein can also be blocked by indirect factors. Some viral proteins form complexes with p53 protein thereby functionally inactivating it, accumulation of wild type p53 in the cytoplasm, over expression of mdm2 protein are also inactivate p53 protein, PTEN mutation leads to an increase of AKT activity, an increase of nuclear mdm2 and impairs p53 response

**Keywords:** TP53 gene, p53 inactivation, mutation, PTEN mutation, mdm2 protein.

## 1. INTRODUCTION

p53 is a tumor suppressor protein and which is encoded by TP53 gene located on the human chromosome 17 (17p13.1). Like other tumor suppressor, the function of p53 to prevent unregulated cell growth, to maintain genomic stability and plays an important role in the protection of our body from cancer [1]. In normal cells, the level of p53 protein is kept low by the combination of another protein called mdm2. This protein binds to p53 preventing its action and transports it from the nucleus to the cytosol and degraded by proteasome under non-stressed conditions [15]. The level of p53 proportionally increases in the response to genotoxic insults such as DNA damage, hypoxia activation, ionizing radiation, oncogene activities, some chemical agents, ribonucleotide depletion, and telomere shortening. Active p53 protein take a role as transcription factor and binds to several genes including WAF1/CIP1 to stimulate the transcription of p21 WAF1/CIP1 protein. p21 / WAF1 also known as cyclin-dependent kinase inhibitor 1. p21 binds to CDK/cyclin complexes (molecules important for the G1/S transition in the cell cycle) inhibiting their activity. This would allow time to repair the DNA. If repair is not possible, p53 stimulates the cell apoptosis (programmed cell death) [2]. In normal cells, regulation of cell division is done by these two proteins but in cancer cells the controls are no longer functioning properly. The mutation of the TP53 gene causes the genetic change and mostly seen in cancer cells. Approximately half of all cases of human cancer attributed to a mutant p53 protein. [2]. TP53 mutations can be within the p53 coding sequence and has a negative effect on the thermodynamic stability of the p53 protein. Unlike most other tumour suppressor genes that are inactivated by frameshift or nonsense mutations, almost 90% of p53 gene mutations are missense mutations in which a single nucleotide is substituted by another. As a result of this, a stable mutant p53 protein is produced with a defective DNA binding domain and accumulating in the nucleus of tumor cells [19]. In addition to the loss of normal regulatory function of p53 protein that a mutation in TP53 may cause, many p53 mutants have positive effects on the development of tumor by several ways [4]. In a heterozygous situation ( both wild type (WT) and mutant alleles exist), expressing both wild-type and mutp53, mutant p53 work against WTp53 tumor suppressor functions. The transcriptional activity of WT p53 is blocked by mutant p53 [5]. Eventually, in the course of tumor progression, the remaining WT TP53 allele is often lost (mostly by deletion), further enhancing tumorigenesis.

## 2. MAJOR FACTORS THAT INACTIVATE p53 REGULATION

P53 protein plays a crucial role in the cell cycle of multicellular organisms, where it is involved in transactivation of a variety of growth-inhibitory signals of cell cycle control, via specific mechanisms. Its inactivation may lead to uncontrolled cell proliferation and a predisposition to abnormal proliferation. [10]

There are several ways that inactivate p53.

### 1. Mutational Inactivation

Inactivation of the p53 gene is essentially due to missense in which a single nucleotide is substituted by another which lead to either expression of a mutant protein (90% of cases) or absence of protein (10% of cases) In a high percentage of human tumors, p53 is always functionally impaired. "The p53 mutational type differs among cancers of the colon, lung, esophagus, breast, liver, brain, reticuloendothelial tissues, and hemopoietic tissues. Transitions predominate in colon, brain, and lymphoid malignancies, whereas G:C to T:A

transversions are the most frequent substitutions observed in cancers of the lung and liver. Mutations at A:T base pairs are seen more frequently in esophageal carcinomas than in other solid tumors. Most transitions in colorectal carcinomas, brain tumors, leukemias, and lymphomas are at CpG dinucleotide mutational hot spots. G to T transversions in lung, breast, and esophageal carcinomas are dispersed among numerous codons". [20]

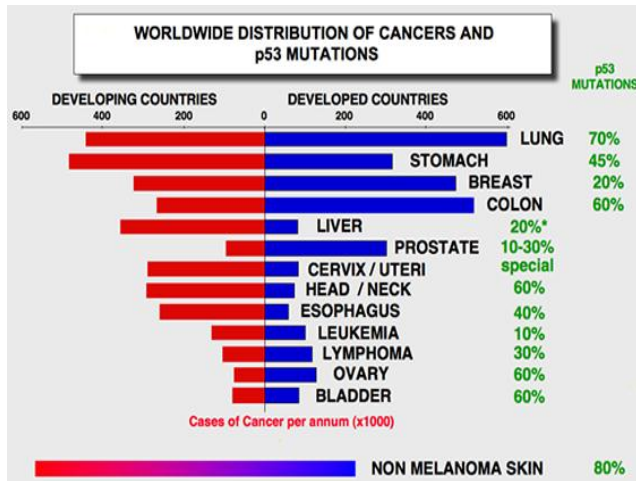


Figure : p53.free.fr

## 2.1. Indirect (Mutation-independent) Inactivation of p53

Viral oncoproteins such as E6 protein (HPV), SV40 Large T antigen, E1B protein (adenovirus), IE84 protein (Human Cytomegalovirus) binds with P53 protein, and functionally inactivating it as a result p53 proteins are degraded [9], [11]. Certain HPV types such as HPV type 16 and type 18 lead to infection of cervix. If not treated they can cause irreversible changes leading to cervical cancer. [6]

## 2.2 Nuclear Exclusion of P53

Molecular and immunohistochemical analyses indicate that wild type p53 accumulates in the cytoplasm, such as, in the case of Inflammatory breast carcinomas (37%) and 95% of undifferentiated neuroblastomas tumour cells have these characteristics, this accumulation causes functional inactivation of p53 [7] [8]. In some breast cancers the wild-type p53 protein is accumulated in the cytoplasm and stabilized. The exclusion of the p53 protein from the cell nucleus inactivates the p53 function (unable to inhibit the cellular proliferation)[7]. Similar case is also observed in normal lactating breast tissue in which accumulation of p53 in the cytoplasm of ductal cells. This observation indicates that estrogen-mediated cell division could involve inactivation of p53 protein via exclusion from the cell nucleus. In this case, the cancer cells might use an altered version of a physiological mechanism to retain p53 in the cytoplasm. "While the mechanism by which the wild-type p53 could be retained in the cytoplasm is not known, an interesting hypothesis derives from the fact that one of the nuclear localization signals is located between amino acid residues 316 and 321. Serine-315 can be

phosphorylated by a cdc2-like kinase. It is therefore possible that a growth-regulatory signal, such as an active cdc2-like kinase, could alter p53 protein via phosphorylation and exclude it from the nucleus” [7]. “The cytoplasmic (wild-type) p53 group had the longest overall survival, with an average of 38 months from the time of diagnosis (45 months if one patient who died immediately after diagnosis is not included), whereas the nuclear (mutant) p53 group had the shortest, with 20 months' survival. Although these data suggest that survival time and estrogen receptor status may correlate well with high levels of wild-type cytoplasmic p53 Protein”[7].“Neuroblastoma cell lines with cytoplasmic p53 showed decreased cell cycle arrest response after DNA damaging treatments. This may result from p53 being excluded from the nuclear compartment, where it normally functions as a transcription factor. Therefore, exclusion of p53 from the nucleus may compromise the ability of p53 to exert its tumor suppressor function and may be an important alternative mechanism of p53 inactivation during tumor development”. [8]

### **2.3 Accumulation of mdm2 Protein**

“MDM2 gene (Murine Double Minute) encodes for a 90-kD protein that forms a complex with p53 protein and inhibits its transactivating properties”. “[10] “The MDM2 protein is one key regulator of p53 activity. MDM2 inhibits p53 activity by two ways. First, MDM2 binds to the N-terminal trans-activation domain (TAD) of p53, preventing transcription of downstream targets. Second, MDM2 functions as an E3 ubiquitin ligase to maintain low protein levels of p53 under non-stressed conditions and to return p53 to normal levels after a damage response is resolved”[15]. “Overexpression of MDM2 in tumor cells including leukemia and lymphomas is reported in several articles, which allows its association with p53, is mainly due to MDM2 gene amplification, but other mechanisms have also been described, including an elevated level of MDM2 mRNA or enhanced levels of translation”. [10]“Although these tumours would be expected to no longer express p53, the opposite situation is generally observed, with a large number of tumours overexpressing both p53 and mdm2. The reasons for this have not been clarified. No formal exclusion between p53 gene mutation and mdm2 accumulation has been clearly demonstrated, suggesting that this situation could be due to an oncogenic activity of mdm2 independent of p53”. [10], [11]

### **2.4 PTEN Mutation**

“Phosphatase and tensin homolog (PTEN) is a protein that, in humans is encoded by the PTEN gene. Mutations of this gene cause development of many cancers. PTEN is a lipid phosphatase that negatively regulates the phosphatidylinositol 3-kinase (PI3K) signaling pathway”[13]. “PI3K–PTEN signaling pathway promotes cell survival and proliferation, increases in cell size and chemoresistance. Each of these biological outcomes results from the interaction of this pathway with other signalling networks”. [13]

“When PTEN is deleted, mutated or inactivated result in activation of PI3K effectors, particularly the activation of the key survival kinase protein kinase B (PKB, also known as AKT) can occur in the absence of any exogenous stimulus, and tumorigenesis can be initiated”. [12,13]

“AKT kinase phosphorylates mdm2 protein and induces its migration into the nucleus where it binds and ubiquitinates p53. Upon growth factor activation, mdm2 activation through

AKT activation ensure proper cell growth. PTEN, a p53 regulated gene, down regulate the AKT pathway. PTEN deletion leads to an increase of AKT activity, an increase of nuclear mdm2 and impairs p53 response”. [13]

## 2.5 AKT Alteration

“The p53 tumor suppressor protein and the Akt/PKB kinase play important roles in the transduction of pro-apoptotic and anti-apoptotic signals, respectively. Phosphorylation of Mdm2 by AKT enables its translocation from the cytoplasm into the nucleus, and the subsequent inactivation of nuclear p53 by Mdm2, mdm2 activation through AKT activation ensure proper cell growth”.[14],[ 15]

“Although no mutation of AKT has been found in human cancer, constitutive activation of its kinase activity has been observed via deregulation of the upstream pathway. An increase of AKT activity leads to an increase of nuclear mdm2 and incapacitates p53 and overcome its pro-apoptotic effects”. [14]

“Akt has been implicated in the down-regulation of p53 via MDM2. Studies have shown that MDM2 is phosphorylated by AKT at different sites, resulting in its stabilization Other studies have shown nuclear translocation of MDM2 in response to phosphorylation by AKT. This results in decreased p53 transcriptional activity from MDM2 binding at the transactivation domain and increases the ubiquitylation of p53”. [ 15]

## 2.5 AKT Alteration

“Two major effectors of cell cycle checkpoint responses are ATM and ATR, protein kinases that phosphorylate cellular substrates in response to various forms of genetic stress. In response to DNA damage , p53 and mdm2 are phosphorylated by two protein kinases the ataxia telangiectasia mutated (ATM) and ATR serine/threonine kinases. This causes dissociation of p53 from mdm2, leading to increased p53 protein levels and transcription of genes leading to cell cycle arrest (p21) or apoptosis”. [16], [17]

“One of the check point is G2 check point (during which the fidelity of DNA replication is assessed and errors are corrected. [17] The G2checkpoint system includes immediate and sustained signaling events to prevent cells from entering mitosis with damaged chromatids. Ataxia telangiectasia (AT) cells with inactivating mutations in ATM displays a defect in G2 checkpoint function, inactivation of G2 checkpoint function thus may contribute to the genetic instability that characterizes cancer”.

“ATM is a high-molecular-weight protein kinase encoded at 11q22-23, ATM can associate with and phosphorylate p53 at serine 15 and is involved in the dephosphorylation of p53 at serine 376, both events are associated with p53 activation. Reduced levels of ATM protein have been detected in tumor cells from 30% to 40% of patients with Chronic Lymphocytic Leukemia”. [18]

## 3.DISCUSSION

TP53 gene contribute to about half of the cases of human cancer, so that mutation in TP53 gene may involve in the initiation of malignant transformation.

Other data in other tumour tissue also suggest that Mdm2 is playing important role in p53 regulation. The results also indicate that MDM2 could be most important inhibitor of p53

even when expressed at low levels. Therefore, MDM2 may play a broader role in the functional inactivation of p53 during tumor development.

Normal lactating breast tissue accumulates p53 in the cytoplasm of ductal cells and similar case seen in some breast cancers the wild-type p53 protein is accumulated in the cytoplasmic compartment of the cell and stabilized. Lactating breast tissue may have some protective mechanism against cancer.

#### **4.CONCLUSION**

Tumor suppressor genes are involved in a diversity of cellular processes such as cell cycle control, replication, recombination, signal transduction, repair, differentiation and aging. One of our guardian gene is p53 Tumor suppressor gene, restrict cell cycle progression, Its control over the cells division is lost with genetic alteration (mutation) or some external factors leading to its inactivation.

TP53 gene contribute to about half of the cases of human cancer. Most of these are missense mutations, changing the information in the DNA at one position and causing the cell to build p53 with an error, mutant p53 unable to stop multiplication in the damaged cell.

The function of p53 protein can also be blocked by indirect factors. Some viral proteins form complexes with p53 protein thereby functionally inactivating it. Another inactivation factor, accumulation of wild type p53 in the cytoplasm. While the mechanism by which the wild-type p53 could be retained in the cytoplasm is not known, 37% of inflammatory breast carcinomas and 95% of undifferentiated neuroblastomas tumour cells have this type of inactivation. Mdm2 is an important negative regulator of p53. Mdm2 protein functions both as an E3 ubiquitin ligase that recognizes N-terminal trans-activation domain (TAD) of the p53 and inhibitor of p53 transcriptional activity. Overexpression of MDM2 is observed in many tumours especially sarcomas, PTEN deletion leads to an increase of AKT activity, an increase of nuclear md

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