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Tumor Protein p53: Novel Aspects of an Old Tumor Marker

Ahmed M. Kabel[1,2,*]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
[2]Department of Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt
*Corresponding author: drakabel@gmail.com

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Abstract P53 gene is a tumor suppressor gene that stops the formation of tumors. If a person inherits only one functional copy of the p53 gene from his parents, he will be predisposed to cancer and usually develop several tumors in various tissues in early adulthood. However, mutations in p53 are found in most tumor types, and so contribute to a number of molecular events leading to tumor formation. There are numerous informations that exist on all aspects of p53 normal function and mutant expression in human cancers, reflecting its key role in the pathogenesis of human cancers.

Keywords: *p53, tumor, marker*

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1. Introduction

Tumor protein p53, also known as p53, is any isoform of a protein encoded by homologous genes in various organisms, such as TP53 (humans) and Trp53 (mice). This gene is crucial in multicellular organisms, where it prevents cancer formation, thus, functions as a tumor suppressor [1]. As such, p53 can be considered as "the guardian of the genome" because of its role in preventing genome mutation [2]. In addition to the full length protein, the human *TP53* gene encodes at least 15 protein isoforms, ranging in size from 3.5 to 43.7 kDa. All these p53 proteins are called the p53 isoforms [1]. It was found that TP53 gene is the most frequently mutated gene (>50%) in human cancer, indicating that the TP53 gene plays a crucial role in preventing cancer formation [3]. TP53 gene encodes proteins that bind to DNA and regulate gene expression to prevent mutations of the genome [4].

2. Structure of P53 Gene

In humans, the TP53 gene is located on the short arm of chromosome 17 (17p13.1). It consists of an acidic N-terminus transcription-activation domain (TAD), also known as activation domain 1 (AD1), which activates transcription factors; activation domain 2 (AD2) important for apoptotic activity; Proline rich domain important for the apoptotic activity of p53 by nuclear exportation via MAPK; central DNA-binding core domain (DBD). Contains one zinc atom and several arginine amino acids, responsible for binding the p53 co-repressor LMO3 [5]; nuclear localization signaling domain; homo-oligomerisation domain (OD) and C-terminal involved in down regulation of DNA binding of the central domain [6].

Mutations that deactivate p53 in cancer usually occur in the DBD. Most of these mutations destroy the ability of the protein to bind to its target DNA sequences, and thus prevents transcriptional activation of these genes. As such, mutations in the DBD are recessive loss-of-function mutations. Molecules of p53 with mutations in the OD dimerise with wild-type p53, and prevent them from activating transcription. Therefore OD mutations have a dominant negative effect on the function of p53 [7].

3. Isoforms of P53

As 95% of human genes, TP53 encodes more than one protein. Until now, 12 human p53 isoforms were identified (p53α, p53β, p53γ, Δ40p53α, Δ40p53β, Δ40p53γ, Δ133p53α, Δ133p53β, Δ133p53γ, Δ160p53α, Δ160p53β, Δ160p53γ). P53 isoforms are expressed in a tissue dependent manner and p53α is never expressed alone [3].

The full length p53 isoform proteins can be subdivided into different protein domains. Starting from the N-terminus, there are first the amino-terminal transactivation domains (TAD 1, TAD 2), which are needed to induce a subset of p53 target genes. This domain is followed by the Proline rich domain (PXXP), which is required among others for p53 mediated apoptosis [8]. Some isoforms lack the Proline rich domain, such as Δ133p53β,γ and Δ160p53α,β,γ; hence some isoforms of p53 are not mediating apoptosis. Afterwards there is the DNA binding domain (DBD), which enables the proteins to sequence specific binding. The carboxyl terminal domain completes the protein. It includes the nuclear localization signal

(NLS), the nuclear export signal (NES) and the oligomerisation domain (OD). The NLS and NES are responsible for the subcellular regulation of p53. Through the OD, p53 can form a tetramer and bind to DNA. Among the isoforms, some domains can be missing, but all of them share most of the highly conserved DNA-binding domain [9].

The isoforms are formed by different mechanisms. The beta and the gamma isoforms are generated by multiple splicing of intron 9, which leads to a different C-terminus. Also, alternative initiation of translation at codon 40 or 160 bear the Δ40p53 and Δ160p53 isoforms [8]. Due to the isoformic nature of p53 proteins, there have been several evidences showing that mutations within the TP53 gene giving rise to mutated isoforms can cause various cancer phenotypes [10].

4. Functions of P53

Functions of p53 are represented in Figure 1. P53 plays a crucial role in apoptosis, genomic stability and inhibition of angiogenesis. In its anti-cancer role, p53 can activate DNA repair proteins when DNA has sustained damage. Thus, it may be an important factor in aging. It can arrest growth by holding the cell cycle at the G1/S regulation point on DNA damage recognition. Also, it can initiate apoptosis if DNA damage proves to be irreversible [11].

Activated p53 binds DNA and activates expression of several genes including microRNA miR-34a [12], WAF1/CIP1 encoding for p21 and hundreds of other down-stream genes. p21 (WAF1) binds to the G1-S/CDK (CDK4/CDK6, CDK2 and CDK1) complexes (molecules important for the G1/S transition in the cell cycle) inhibiting their activity. When p21 (WAF1) is complexed with CDK2 the cell cannot continue to the next stage of cell division. A mutant p53 will no longer bind DNA in an effective way, and, as a consequence, the p21 protein will not be available to act as the "stop signal" for cell division [11]. P53 expression can be stimulated by UV light, which also causes DNA damage. In this case, p53 can initiate events leading to tanning [13].

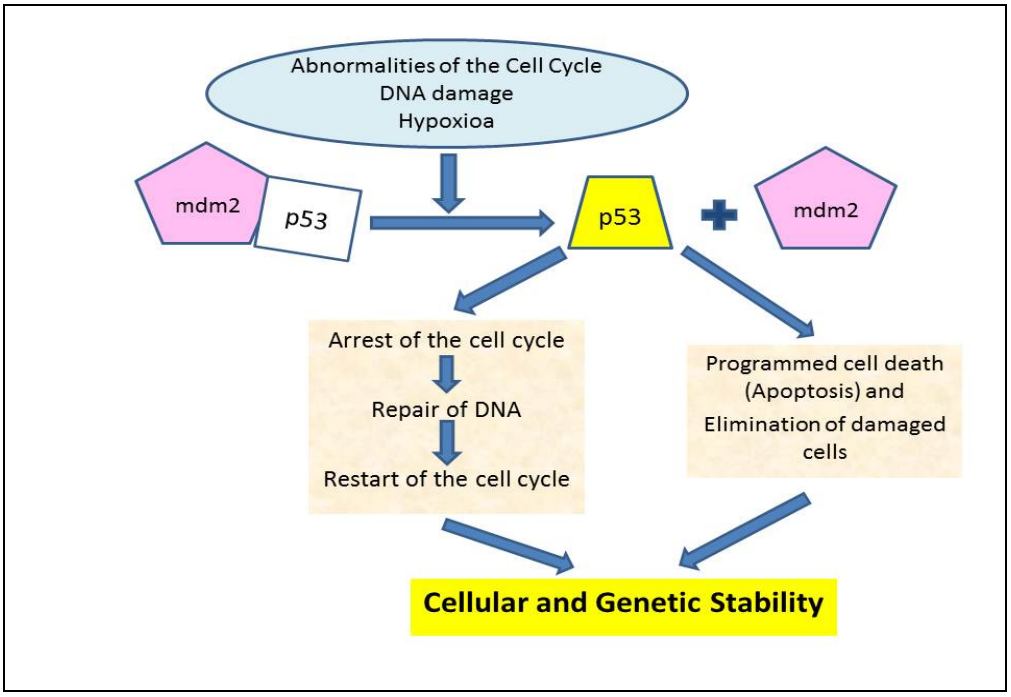

Figure 1. Functions of p53

5. Regulation of P53 Expression

P53 is activated in response to DNA damage (induced by radiation or chemical agents such as hydrogen peroxide), oxidative stress, osmotic shock, ribonucleotide depletion, and deregulated oncogene expression [14]. This activation is marked by two events. First, the half-life of the p53 protein is increased leading to accumulation of p53 in stressed cells. Second, a conformational change forces p53 to be activated as a transcription regulator in these cells. The critical event leading to activation of p53 is the phosphorylation of its N-terminal domain [15].

Phosphorylation of the N-terminal end of p53 disrupts mdm2-binding. Other proteins, such as Pin1, are then recruited to p53 and induce a conformational change in p53, which prevents Mdm2-binding even more. Phosphorylation also allows for binding of transcriptional coactivators, like p300, which then acetylate the carboxyl-terminal end of p53, exposing the DNA binding domain of p53, allowing it to activate or repress specific genes. Deacetylase enzymes, such as Sirt1 and Sirt7, can deacetylate p53, leading to an inhibition of apoptosis. Some oncogenes can also stimulate the transcription of proteins that bind to mdm2 and inhibit its activity [16].

6. Role of P53 in Disease

If the TP53 gene is damaged, tumor suppression is severely compromised. People who inherit only one functional copy of theTP53 gene will most likely develop tumors in early adulthood, a disorder known as Li-

Fraumeni syndrome. The TP53 gene can also be modified by mutagens (chemicals, radiation, or viruses), increasing the likelihood for uncontrolled cell division. More than 50 percent of human tumors contain a mutation or deletion of the TP53 gene [17]. Induction of p53 expression seems to be a solution for treatment of tumors or prevention of metastasis. Research showed that restoration of normal p53 function can lead to regression of certain cancer cells without damaging other normal cells [18].

Certain pathogens can also affect the p53 protein that the TP53 gene expresses. For example, human papillomavirus (HPV), encodes a protein, E6, which binds to the p53 protein and inactivates it [19]. This mechanism, in synergy with the inactivation of the cell cycle regulator pRb by the HPV protein E7, allows for repeated cell division manifested clinically as warts. Certain HPV types, in particular types 16 and 18, can also lead to progression from a benign wart to low or high-grade cervical dysplasia, which are reversible forms of precancerous lesions. Persistent infection of the cervix over the years can cause irreversible changes leading to carcinoma in situ and eventually invasive cervical cancer [20].

The p53 protein is continually produced and degraded in cells of healthy people. This degradation is associated with binding of mdm2. In a negative feedback loop, mdm2 itself is induced by the p53 protein. Mutant p53 proteins often fail to induce mdm2, causing p53 to accumulate at very high levels. Moreover, the mutant p53 protein itself can inhibit normal p53 protein levels. In some cases, single missense mutations in p53 have been shown to disrupt p53 stability and function [21].

7. Conclusion

P53 is a gene that codes for a protein that regulates the cell cycle and hence functions as a tumor suppressor gene. It is very important for cells in multicellular organisms to suppress cancer. It has many isoforms that may have diverse effects on different types of cancer. Further study of these isoforms may carry a new hope for prevention and treatment of various types of tumors.

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