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REVIEW ARTICLE

The tumor suppressor gene TP53 and colorectal cancer: A review

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Abstract
TP53 is a gene and the p53 is its protein product. It is well known as a tumor suppressor gene, due to its inherent property of apoptosis and its role in the suppression of tumor formation. Its oncogenic property is due to p53 mutation. This oncogenic property is named "gain of oncogenic property". The functions of p53 have been studied the world over, especially the oncogenic function. It is well known for its role to induce apoptosis, but now it is established that it is also a key player in cell cycle regulation. It controls and monitors the cell division, chromosomal segregation, and cellular senescence. Due to all these important cellular functions, this protein is labeled as the "guardian of the genome". The p53 protein is a nuclear phosphoprotein. It is composed of 393 amino acids. The structural and functional domains are an N-terminal transactivation domain, a protein-rich regulatory domain, and a C-terminal domain involved in the regulation of DNA binding. The colorectal cancers (CRC) are a major cause of morbidity and mortality world over. This is the third most common cancer worldwide and the fourth most common cause of death. Although it is slow-growing cancer the five-year survival is low. It is a heterogeneous disease and is due to, a complex genetic and biochemical interplay. This review summarizes the functions of p53 and its role in CRC.
Keywords: TP53, p53, colorectal cancers, CRC, Tumor suppressor gene, apoptosis, cellular senescence, guardian of the genome

1 | INTRODUCTION

It is a fact that there is a presence of the mutation in p53 in the majority of colorectal cancers. The growth of CRC cell lines in vitro could be suppressed by the introduction of wild-type p53. It thus establishes the tumor suppressor property of this gene. [1] The p53 is classified as cellular SV40 large T antigen-binding protein. [2-3] it is a stress-inducible transcription factor. It regulates a large number of diverse downstream genes to exert a regulatory function. The status of p53 mutation is closely related to the progression and outcome of the sporadic CRC.

The p53 structure:

TP53 is a gene and p53 is its product protein. In 1979 it was first identified as a transformation-related protein and as a cellular protein that was accumulated in the cancer cells. It is found weakly oncogenic. The oncogenic property is due to p53 mutation. This oncogenic property was named later on as "gain of oncogenic function". [4] The scientists all over the world have studied extensively its function and its role in cancer. Its primary role is to induce apoptosis, but now it is established that it is also a key player in cell cycle regulation, development, differentiation, gene amplification, DNA recombination, chromosomal segregation, and cellular senescence. Due to all these important cellular functions, this protein is aptly labeled as "the guardian of the genome". [5]

The structure of the TP53 gene:

The *TP53* is a gene and p53 is its protein. It is the "guardian of the genome" because it plays an essential role in cell cycle regulation. It controls and monitors the cell division. [6] The p53 is a homo-tetramer, consisting of 393 amino acids. The N-terminal region contains the transactivation domain, which is further divided into two subdomains and is followed by a Proline-rich region important for apoptotic activities. [7] The human TP53 gene spans 20kb on chromosome band 17p13.1. This gene is composed of 11 exons. The first of them is non-coding. Its promoter harbors several consensus binding sites and does not contain a TATA box. The expression of TP53 is constitutive and ubiquitous. The protein regulation takes place at the post-translational level. [8]

The p53 protein is a nuclear phosphoprotein. It is composed of 393 amino acids. The structural and functional domains are an N-terminal transactivation domain, a protein-rich regulatory domain, and a C-terminal domain involved in the regulation of DNA binding. In the cancers the most common mutations alter this structure either by abrogating protein-DNA contacts or by disrupting protein folding [9] Once it is activated, this protein escapes degradation and gets accumulated in the nucleus. It also becomes active due to conformational changes, which activates its capacity to transactivate target genes. The accumulation of p53 is controlled by mdm2. The mdm2 is an ubiquitin ligase that directs p53 out of the nucleus, where it is degraded. [10]

The p53 protein is activated by several factors like Gamma or UV radiation, free radical damage, alkylating agents, Aflotoxins, and benzopyrines, etc. It is also activated by agents that cause damage to the mitotic spindle, ribonucleotide depletion, heatstroke, and hypoxia. The independent pathways for the activation have also been identified that are dependent on the upstream regulatory kinase. [11]

The functions of p53:

1. Apoptosis:

In 1970, Kerr *et al* coined the term apoptosis. This word is derived from the Greek meaning "dropping off" and it refers to the falling of leaves from the tree in autumn. Since then it remains one of the most investigated processes in biological research. [12] During the process of apoptosis chromatin condensation and nuclear fragmentation occur along with Pyknosis. [13] The chromatin breaks up inside the cell; a process called karyorrhexis. The morphology of the cell also changes with membrane blebing, ultra-structure modification of cytoplasmic organelle and membrane integrity, and the phagocytes engulf the apoptotic cell. [14]

2. Senescence:

There is an irreversible arrest of cell proliferation. This process is called senescence. This is one of the most important barriers to malignant tumorogenesis. [15]

3. Cell migration:

Cell migration is another tumor suppressor activity of p53. This activity is due to the inhibition of philopodia formation. [16]

P53 and tumorogenesis:

Supplementary information The online version of this article (https://doi.org/10.15520/ijmhs.v10i09.3100) contains supplementary material, which is available to authorized users.

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The evolution of cancer cells from the normal cell is a complex process. It is a result of multiple genetic and epigenetic alterations. These alterations confer a selective advantage upon the altered cell. These altered cells are bestowed with the property of self-sufficiency of growth signals, evasion of programmed cell death, unlimited replicative potentials, and finally the ability to invade and metastasize. [17] It has been observed that more than 50% of cancer patients have a somatic mutation of the TP53 gene. These are missense mutations. This loss of function of p53 causes genomic instability, the potential for metastasis, resistance to chemo and radiotherapy, poor patient survival, and tumor progression. [18] The other activities which support the process of tumorogenesis are the dominant-negative (DN) activity of mutant p53. [19] Due to the dominant-negative activity, the p53, loses its tumor suppressor function and leads to accelerated tumor progression. [20]

The Colorectal cancers:

The Vogelstein lab used colorectal cancer (CRC) as a model system for the study of genetic alterations that leads ultimately to cancer development. [21]This lab analyzed the different stages of CRC starting from adenoma to carcinoma and metastasis. This revealed a multistep progression model. It established that colorectal tumorogenesis has a clonal nature and the p53 is usually inactivated at the transition from late adenoma to carcinoma. It also shows that the tumorogenesis is a result of the accumulation of various mutagenic changes in the cell. Colorectal cancer is the third most common cancer worldwide in men and the second most common in females. Its prevalence is rising gradually and the five-year survival rate is poor. There were nearly 14.1 million cases and 694000 deaths globally in 2012. It has shown a rising trend in Asian countries too such as China, Japan, South Korea, and Singapore with a two to four-fold increase in the last decade. [22]

P53 mutation in CRC:

The evolution of colorectal cancers is a multistage process that involves the inactivation of the tumor suppressor gene and the activation of the oncogene. It has been confirmed by the numerous studies that p53 plays a central role in defending our body from the development of cancers. It acts as a key tumor suppressor gene. [23] It is also known that the progression of CRC follows the mutation of the APC, K-Ras, and p53 genes. [24]The p53 is the most commonly mutated gene in human cancers.[25]The mutation of p53 plays a central role in the adenoma-carcinoma transition during the pathological process.[26]The mutation of p53 occurs in 34% of the proximal colon tumors and 45% in the distal colorectal tumors.[27]

The mutation occurs in exon 5 to 8 which is the DNA binding domain. It is mainly in some of the hotspot Condons, such as 175,245,248,273 and 282, comprising of G to A, C to T transition, and leading to the substitution of a single amino acid in p53 protein. These substitutions cluster in the DNA binding domain and disrupt specific DNA binding and sequential transactivation. The different types of p53 mutations determine the invasive depth, metastatic site, and even the prognosis of the patients. Its mutation is associated with lymphatic invasion in proximal colon cancers and shows a significant correlation with both lymphatic and vascular invasion in distal CRC. It is seen that the patient with p53 mutations are more chemo-resistant, and show a poorer prognosis as compared to wild p53. [28] It has also been found by colorectal cancer international collaborative study, that the patients with mutant p53 in exon 5 had worse outcome for the proximal colon cancers. In the advanced stage tumors, the inactivating mutation of p53 occurred more frequently and also they are associated with the worst prognosis. [29]

Routine testing of p53 mutation, is there is any role?

A major discussion is whether the practicing oncologist should undertake the testing of p53 mutation as a routine in the management of CRC? The answer is **NO**. It is because p53 mutation has a non-significant trend towards worse survival that too in more distal tumors. This result is generally consistent with previous retrospective analyses. [30-31]

The prognostic value is also modest. The testing for p53 mutation could be of value if it showed enough predictive power to help identify tumors more responsive to specific anti-Neoplastic treatment. The study of p53 as a marker is interesting but it is not

changing the existing clinical practice. Ultimately before a marker is adopted as a valuable prognostic or predictive tool, it needs to be standardized and validated prospectively, preferably as a part of a randomized trial. It is also very important that it should contribute to improving the management and treatment selection of the patients. The testing for p53 mutation remains of interest in the field of cancer research, but its routine use is not recommended in the patient's management.

2 | DISCUSSION

The human TP53 gene is located on chromosome 17p and consists of 11 exons and 10 introns. [32] The wild type p53 consists of 393 amino acid residues and many functional domains. The p53 is aptly labeled as a guardian of the genome because it carries out many functions besides apoptosis. It also causes irreversible arrest of cell proliferation, a process called senescence. The evolution of cancer cells from the normal cell is a complex process. It is a result of multiple genetic and epigenetic changes. The altered cells are bestowed with the property of self-sufficiency in growth signals, evasion of programmed cell death i.e. apoptosis, unlimited replicative potentials, and the ability to invade and metastasize. In colorectal cancers, the p53 is inactivated at the transition from late adenoma to carcinoma. The tumorogenesis is a result of the accumulation of various mutagenic changes in cells.

The CRC is also divided into proximal colon cancer (before the splenic flexure), distal colon cancer (after the splenic flexure), which includes rectal cancer. The origin of the proximal gut is from the midgut and the distal colon and rectum originate from the hindgut. The innervations and blood supply are also different [33] It is thus natural to found different genetic abnormalities in the CRC of different sites, and so the biology, prognosis, and response to treatment also differ, in CRC originating in the left versus the right side. The mutation of p53 occurs in 34% of the proximal colon cancers and 45% in distal colorectal cancers. In the advanced stage tumors, the inactivating mutation of p53 occurred more frequently and also they are associated with the worst prognosis.

The burning question is whether the oncologists should undertake the testing of p53 mutation as a routine in the management of colorectal cancers? The definite answer is NO. It is because p53 mutation has a non-significant trend towards worse survival that too in more distal tumors. The significance of this discussion is to open a whole new domain in research, prognostication, and management of colorectal cancers. Defining the molecular biology of CRC helps in a better understanding of the disease. It also helps to guide the therapy and provide both prognostic and predictive information. The ultimate goal of studying the molecular background of CRC is to find a consensus of treatment in different types of colorectal cancers.

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