Review Article

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P53 and the Carcinoma of the Breast: A Review

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Abstract

TP53 is a gene and p53 is its product protein. Since its discovery many studies have looked into its function and its role in cancer. It is not only involved in the induction of apoptosis but is also, a key player, in cell cycle regulation, development, differentiation, gene amplification, DNA recombination, chromosomal segregation and cellular senescence and so, it is called "the guardian of genome". The human TP53 gene spans 20kb on chromosome band 17p13.1. The biological functions of p53 are apoptosis, senescence and cell migration. The evolution of a normal cell towards a cancerous one is a complex process. Tumorogenesis is considered to endow, the evolving tumor with, self-sufficiency of growth signals, insensitivity to antigrowth signals, evasion from programmed cell death, unlimited replicative potentials and finally the ability to invade and metastasize. TP53 may be considered as the "ultimate tumor suppressor gene". Its oncogenic activity is attributed to loss of function, dominant negative (DN) oncogenic properties and activities of mutant p53. In breast cancer its oncogenic function is due to p53 mutation, changes in- upstream regulatory pathways, in p53 transcriptional target genes, in p53 co-activators, and/or involvement of other family members of p53 family like p63 and p73. The p53 mutation is present in only in about 20% of breast cancers, but when present, they entail the worst prognosis. This interesting paper is a review and discussion about role of p53 in carcinoma breast.

Keywords: p53, Oncogenesis, Tumor Suppressor Gene, Carcinoma Breast, Guardian of Genome, Apoptosis

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Introduction

The p53 structure

TP53 is a gene and p53 is its product protein. The p53 was first identified in 1979 as transformation related protein and a cellular protein accumulated in the cancer cells, binding tightly to the simian virus 40 (SV40) large T antigens. Initially found to be weakly oncogenic. It was later discovered that the oncogenic property was due to a p53 mutation or what was later called a "gain of oncogenic function".[1]

Since its discovery many studies have looked into its function and its role in cancer. It is not only involved in the induction of apoptosis but is also a key player in cell cycle regulation, development, differentiation, gene amplification, DNA recombination, chromosomal segregation and cellular senescence and so it is called "the guardian of genome".[2,3]

The human TP53 gene spans 20kb on chromosome band 17p13.1. The gene is composed of 11 exons, the first of which is non- coding. Its promoter does not contain TATA box but harbors a number of consensus binding sites. For common, transcription factors such as Spl, NF-kappaB or C-Jun. Despite these potential sites for transcriptional regulation, the expression of TP53 is constitutive and ubiquitous, most of the protein regulation taking place at the post translational level.

The p53 protein is a nuclear phosphoprotein, composed of 393 amino acids in human. It has five structural and functional domains i.e. an N-terminal transactivation domain, a protein rich regulatory domain, an oligomerization domain and a C-terminal domain involved in the regulation of DNA binding. The most common mutation that occurs in cancer alters this structure either by abrogating protein-DNA contacts or by disrupting protein folding.[4]

In most cells the p53 is almost undetectable because it is rapidly degraded by the proteosome. Upon activation, the protein escapes degradation and accumulates in the nucleus. At the same times it is turned from latent to active form by conformational changes which activate its capacity to transactivate target genes. The main factor controlling p53 accumulation is mdm2; a protein encoded by a gene which

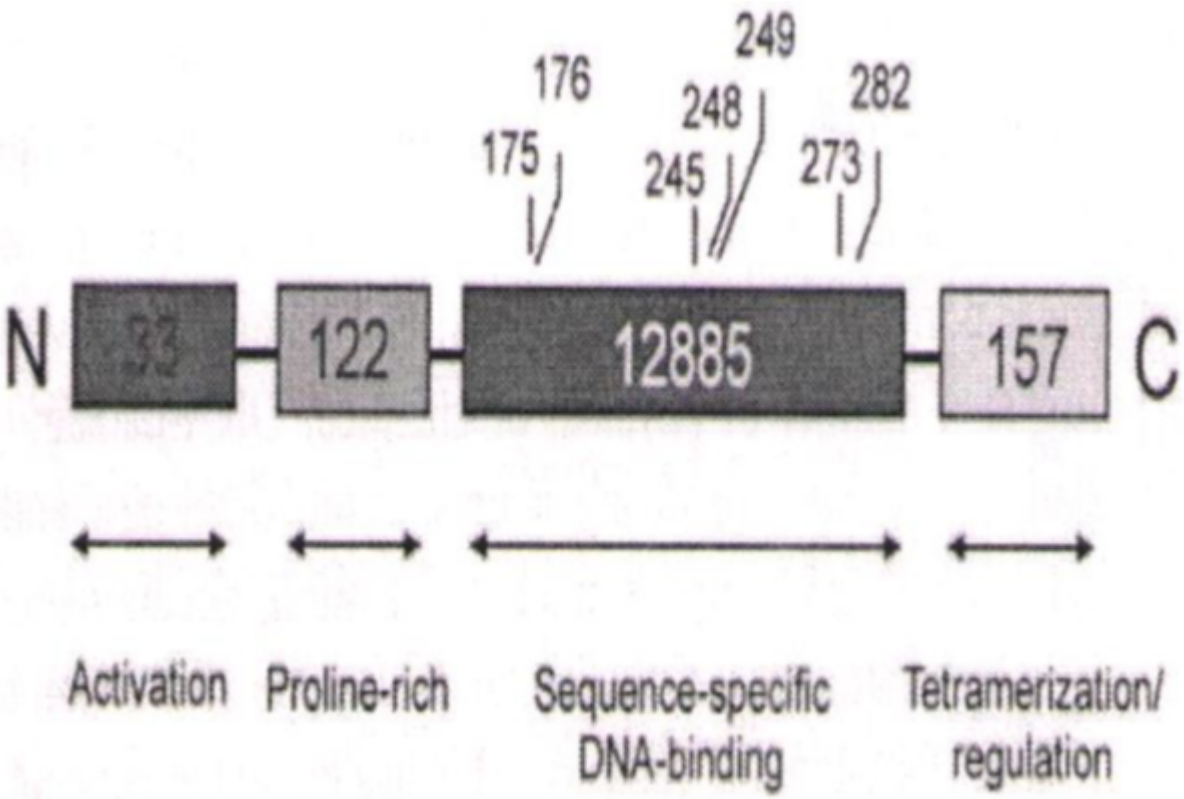

Figure 1: P53: the guardian of Genome

target of p53. Mdm2 acts as an ubiquitin ligase to direct p53 out of the nucleus to proteosome, where it is degraded. [5]

There are several factors which can activate p53 protein like Gamma or UV radiation, free radical damage, mutagens like Aflotoxins, benzopyrines, alkylating agents, agents that cause damage to mitotic spindle, ribonucleotide depletion, hypoxia, heat stroke, exposure to nitric acid etc. Several independent pathways for p53 activation have been identified that appears to be dependent on distinct upstream regulatory kinase.[6]

These include an ataxia-telangectasia mutated (ATM)/ human homologue of rad53(Chk2)-dependent pathway activated by DNA double strand breaks, a second pathway dependent on the alternative product of the INK4 gene, p14ARF (which is activated by expression of oncogene), and a third pathway whose activity is increased by cytotoxic anti-tumor agents and ultraviolet light, but is independent of ATM, Chk2 and p14ARF , activation of this pathway may be mediated by other kinase such as the ATM relative ataxia-telangectasia and Rad3-related protein (ATR).

P53 function

Apoptosis

The term apoptosis is derived from the Greek word meaning "dropping off" and refers to falling of leaves from tree in autumn. Ever since apoptosis was described by kerr et al in 1970, it remains one of the most investigated processes in biological research. [7]

Morphological hall mark of apoptosis in the nucleus is chromatin condensation and nuclear fragmentation which are accompanied by rounding up of cells, reduction in cellular volume (Pyknosis) and retraction of pseudopodia. [8] The chromatin further condenses until it breaks up inside a cell with an intact membrane, a feature called karyorrhexis. [9] In the later stage of apoptosis some of the morphological feature includes membrane blabbing, ultrastructul modification of cytoplasmic organelle and a loss of membrane integrity; the phagocytic cells engulf apoptotic cells. The biochemical changes seen during apoptosis consist of activation of caspase, DNA and protein breakdown, membrane changes and recognition by phagocytic cells. [10]

Senescence

Cellular senescence refers to the essentially irreversible arrest of cell proliferation (growth). It is established and maintained by at least two major tumor suppressor pathways, the p53/p31 and p16NK4a/pRB pathways, and is now recognized as a formidable barrier to malignant Tumorogenesis.[11]

Cell migration

Another tumor suppressor activity of p53 which is still poorly understood is its ability to modulate cell migration. Roax and co-workers have shown that p53 inhibits Cdc-42 induced philopodia formation.[12] Thus p53 causes inhibition of cell cycle; it is apoptosis regulator, helps in DNA repair and inhibitor of angiogenesis and metastasis.

P53 and Tumorogenesis

The evolution of a normal cell towards a cancerous one is a complex process, accompanied by multiple steps of genetic and epigenetic alterations that confer selective advantages upon the altered cells. The alterations underlying Tumorogenesis are considered to endow the evolving tumor with, self-sufficiency of growth signals, insensitivity to antigrowth signals, evasion from programmed cell death, unlimited replicative potentials, and finally the ability to invade and metastasize.[13]

TP53 is special among cancer genes in at least three aspects i.e.

1. Most of its alterations in cancer are missense mutations. This is uncommon for suppressor genes, which are classically inactivated by deletion or non-sense mutations.

2. It is altered at a significant frequency, between 20 to 80%, in almost every human cancer, irrespective of the organ site or the histological type. This observation stresses the central role of p53 as one of the basic elements of the cellular growth control machinery.

3. The protein itself is essential for many aspects of normal life. TP53 may be considered as the "ultimate tumor suppressor gene", the function of which is essentially to protect the cell against the occurrence and development of cancers.[14] Its oncogenic activity is attributed to loss of function, dominant negative (DN) activity of mutant p53 and oncogenic properties of mutant p53.

Loss of function

More than 50% of cancer patients harbor somatic mutation on p53 gene and about 80% mutations are missense mutations. The germ line p53 mutation causes a rare type of cancer predisposition disorder called Li-Fraumeni syndrome (LFS). Both somatic and germ line mutations are usually followed by loss of heterozygosity (LOH) during tumor progression, which results in the inactivation of the remaining wild type alleles of p53. So the loss of function of p53 causes genomic instability, metastasis, resistance to chemotherapy and radiotherapy, poor patient survival and tumor progression.[15,16]

Dominant negative (DN) activity (of mutant p53)

In a heterozygous situation, where both wild type (WT) and mutant alleles exist, mutant p53 can antagonize WT p53 tumor suppressor functions in a dominant negative (DN) manner. The inactivation of the WT p53 by the mutant p53 in a DN mechanism stems from the fact that the transcriptional activity of p53 relies on the formation of tetramers, whose DNA binding function may be interfered by mutant p53.[17,18]The mutated p53 is over expressed in human tumors. This mutant p53 not only loses its tumor suppressive function but also has dominant negative activity on remaining wild type p53. It leads to accelerated tumor development and its growth.[19]

Oncogenic properties of mutant p53

Mutant p53 acquires oncogenic properties that lead to "gain of function" (GOF). Several mechanisms are attributed to this "gain of function" phenomenon. Like;-

- Mutant p53 can inhibit the function of the p53 family proteins i.e. p63 and p73 by protein to protein interaction. It is found that mutant p53 inhibits p73 and p63 only when it is present in excess, a situation which is common in tumors.[20]

- Regulation of gene transcription by mutant p53 is an important "gain of function" mechanism. Mutant p53 have the ability to activate the transcription of multi drug resistance 1 (MDR 1) gene, which causes drug resistance in mutant p53 expressing cancer cells. Besides MDR 1 mutant, p53 has been implicated in the transcriptional regulation of several genes including PCNA, c-myc, FAS, bcl-x1 and VEGF. The transcriptional regulation of these specific genes by mutant p53 may be modulated through preferential binding to structural DNA motif such as non-B DNA structures.[21]

- Mutant p53 inhibits the DNA repair pathway and thus have "gain of Function" and genetic instability.[22]

Mechanisms of inactivation of p53 in breast cancers

p53 mutation

The overall frequency of p53 mutation in breast cancer is around 20%.[23] Certain type of disease is associated with higher frequencies. For example, a number of studies have identified an increased rate of p53 mutation in cancer arising in carriers of germ line BRCA1 and BRCA2 mutations.[24,25] *Moreo*ver a distinct spectrum of p53 mutations occurs in such carcinomas. Strikingly in typical medullary breast carcinoma, p53 mutation occurs in 100% cases. This is of particular interest, since it is now well recognized that medullary breast cancers share clinicopathological similarities with BRCA1 associated cases. Indeed, methylation dependent silencing of BRCA1 expression occurs in medullary breast cancers.[26] *Th*e importance of p53 as a cardinal player in pro-

tecting against cancer development is further emphasized by Li-Fraumeni syndrome (LES), a rare type of cancer predisposition syndrome associated with germ line TP53 mutations.[27] This implies an important role for p53 inactivation in mammary carcinogenesis, and the structure and expression of p53 has been widely studied in breast cancer. In early studies expression of mutant p53 was demonstrated in breast cancer cell lines.[28] Loss of heterozygosity (LOH) in the p53 gene was shown to be a common event in primary breast carcinoma.[29] One more common mutation is coding mutation in p53 in breast cancers, although not ubiquitous.

P53 pathways in breast cancer

It is interesting to note that the frequency of mutation of p53 is significantly lower in breast cancers as compare to many other cancers. Many studies have revealed that there exists a potential mechanism for p53 inactivation independent of mutations. Subsequently alternations have been identified both in upstream regulatory proteins and in downstream p53-induced proteins that may disable or compromise the pathway in breast cancer, but lacking mutation in p53.

Changes in upstream regulators of p53

It has been seen that mutations in other genes also contribute significantly to hereditary breast cancer. For example ATM gene (Ataxia-telangectasia mutated). A-T patients have high incidence of cancer and some develop breast carcinomas.[30] In a large series of breast cancer patients it was found that there exists heterozygosity for truncating mutations in approximately one in 50 patients, consistent with the hypothesis that A-T heterozygote are more common in breast cancer patients than in the general population. It has been hypothesized that inactivation of ATM may be an alternative to p53 mutation in leukemia. There is evidence that low or absent expression of ATM occurs commonly in sporadic breast cancers.[31]

A second protein operating upstream to transduce DNA damage to phosphorylation of p53 is Chk2. Chk2 is activated (by phosphorylation of threonine 68) by ATM in response to double strand breaks and, in turn, catalyses phosphorylation of p53 at serine 20. Analysis of Chk2 sequence in Li-Fraumeni families lacking p53 mutations identified heterozygous germline mutations in some cases, suggesting that Chk2 is a human tumor suppressor gene and implying that loss of function in chk2 might be equivalent to p53 mutation.

Changes in p53 transcriptional target genes

The expression of Mdm2 is directly upregulated by wild type of p53. Amplification and over expression of Mdm2 is a recognized mechanism of p53 inactivation. But its amplification is infrequent event in breast cancers.[32] A second mechanism to promote Mdm2 dependent p53 degradation involves loss of p14ARF either by mutation, deletion or epigenetic silencing. Mutation and deletion in p14ARF are uncommon in breast cancers, but absent or reduced expression occurs in a subset of cases and this is associated with aberrant hypermethylation of the p14ARF promoter. Inactivation is frequently seen in cases with p53 mutation, implying that loss of p14ARF expression is not functionally equivalent to mutation of p53; nevertheless, these results suggest a role for p14ARF inactivation in breast cancers.

One of the most commonly deleted chromosomal regions in breast cancer is 11q23-q25, which contains a number of putative tumor suppressor loci, including ATM, CHK1, PPP2R1B and PIG8. A recent study of structure of these genes in early onset breast cancer determined that the gene most frequently mutated in this region was PIG8, a gene induced by p53 and a putative mediator of p53-dependent apoptosis.[33] Loss of PIG8 function via inactivating mutations thus represents a further potential mechanism by which p53-dependent apoptosis can be impaired in breast cancers.

Changes in p53 co-activators

In addition to proteins such as ATM, ATR and Chk2 that regulate the stability and function of p53 through phosphorylation, a second, functionally distinct, group of proteins is now emerging that appears to operate as cofactor stimulating one or more of the wild-type properties of p53. One such family with possible involvement in breast cancer is the apoptosis stimulating protein of p53 (ASPP). The ASPP family consists of two separate genes i.e. ASPP1 and ASPP2.[34] Expression of either ASPP1 or ASPP2 stimulates the proapoptotic function of wild-type p53 by increasing p53 dependent induction of apoptotic effectors such as Bax and PIG3. In primary breast cancers lacking p53 mutations, expression of both ASPP1 and ASPP2 was reduced. These observations suggest that downregulation of ASPP proteins attenuates p53 dependent apoptosis, thus conferring a selective advantage to breast carcinomas with intact p53. The DNA binding and therefore the transcriptional activating function of p53 is potentiated by acetylation of lysine residue in c-terminus of the protein. This is accomplished by the Histone acetyltransferase p300. Truncating mutations in p300 has been found in breast cancer cell lines and primary cancers.[35]

Other p53 family members

P53 have two structural and functional homologue i.e. p63 and p73. Mutations in p73 are uncommon in human neoplasia. A subset of cases in breast cancer overexpress p73, and in one study this was associated with lymph node metastasis, vascular invasion and high grade malignancy.[36] Analysis of p63 in breast tissue revealed that expression, specifically of the transdominent DNp63, is restricted exclusively to myoepithelial cells. Indeed, p63 has been proposed as a specific and sensitive marker for myoepithelial cells.[37]

P53 and prognosis

The presence p53 mutation relates to an aggressive breast cancer and worst survival. [38] This association was confirmed in a comprehensive meta-analysis of the effect of somatic p53 mutations on prognosis in breast cancers. [39] Potential correlation exists between the type of p53 mutation and clinical phenotype. The mutation affecting amino acids critical for DNA binding was associated with very aggressive cancers, whereas null mutations and other missense mutations were associated with an indeterminate phenotype. A recent study suggests that p53 mutation may be an important molecular genetics correlate of breast cancer progression. [40] P53 mutation can be detected in peripheral blood in a significant proportion of patients whose primary tumor contains mutations. The presence of p53 mutations in plasma DNA is a significant prognostic factor. [41] In breast cancer, it has been seen that specific mutations correlate with primary resistance to Doxorubicin and that presence of such mutation may be predictive of early relapse. [42]

Conclusion

The p53 and its actions has become an interesting molecule for biologists, oncologist and a plethora of scientists. Its pathways, actions, are being explored to understand the mechanism of carcinogenesis as well as to develop strategies to counter it. The inactivation of WT p53 is very diverse with regards to the type and location of the mutations, the type of cancers in which it is involved, the chronology of the mutation along the Tumorogenesis process, and its contribution to the distinct steps of malignant progression. This diversity represents an infinite number of ways in which a p53 mutation might be selected during cancer progression, affected by many factors such as oncogenic stress, specific carcinogens, LOH, DN and GOF advantages and much more. Abundant data from mechanistic, molecular, pathological and transgenic animal studies support an important role for p53 in mammary carcinogenesis. However, despite the convincing evidence implicating loss of function of p53 in breast neoplasia, mutations in the gene occurs at a significantly lower frequency than in other common solid tumors. Molecular pathological analysis of specific components of the p53 pathway is likely to have diagnostic and prognostic utility in breast cancer. The utility of present knowledge is far from satisfactory. The conventional modalities of treating cancers by radiotherapy or chemotherapy kill both normal and cancerous cells with very disturbing and many times unacceptable side effects. When this knowledge becomes tailor made, to treat individual breast cancer, the answer lies in future.

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