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Association of Tumor Suppressor Protein (TP53) in the Progression of Breast Cancer

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Abstract:- The most frequent genetic alteration in human cancer is TP53 mutation. TP53 mutation in breast cancer is linked to more aggressive disease and the worst overall survival rate. Compared to other solid tumours, breast cancer has a lower mutation frequency. Breast cancer treatment may benefit from molecular pathological analysis of the structure and expression of the TP53 pathway's components for diagnosis, prognostic evaluation, and, ultimately treatment. In some studies, the TP53 mutation has been linked to a good prognosis, while in other studies, it has been linked to a poor prognosis. The fact that the studies were conducted on various tumour types and with various therapy regimens may be the cause of these disparate results. The apoptosis, cell cycle arrest, and senescence in response to stress are the main topics of this review of recent developments in TP53 research. We also go over TP53-prevalence, prognosis and detection of the mutation for treating human cancer. Methods: Literature review of English language papers available through PubMed and Google Scholar.

Keywords:- *TP53, Breast Cancer, Mutation, Mutant P53, Human Cancers.*

I. INTRODUCTION

Every year, more than one million people are affected by breast cancer with a leading cause of mortality. Various clinical and biological factors like age at the time of diagnosis, histological grading and size of the tumor, nodal status, expression of estrogen /progesterone receptor, and Her2 status determines the prognosis of localized breast cancer. Treatments involve surgical removal of tumor, radiation therapy of the breast, Hormone therapy, and chemotherapy.

Gene panel testing in breast cancer has been widely used for women early diagnosed with breast cancer and for women who are unaffected but have a strong family history of breast cancer. BRCA1 and BRCA2 gene mutations are the most common genetic explanation for those with a strong family history of breast cancer. [3]

The TP53 gene known as ‘the guardian of the genome’ is a crucial tumor suppressor gene. The TP53 gene encodes the protein p53 is one of the most frequently mutated genes among human cancers. It is reported that approximately half of all cancers have inactivated p53 [**1]**

The cellular tumor antigen protein p53 acts as a checkpoint to control DNA damage. It activates downstream genes to repair the damage or initiates apoptosis. Somatic mutations in TP53 are very common in the formation of many cancer types. Germline mutations cause a familial cancer predisposition. The syndrome was first observed in 1969 by Li and Fraumeni who described soft tissue sarcomas in children of four families [**2].** Mutation carriers have a very high risk of malignancy during their lifetime. Germline mutations in the TP53 gene may cause an even higher risk of breast cancer malignancy, but these are much rarer than mutations in BRCA1 and BRCA2 **[1].**

In this review we summarized structure and functions of the TP53 and its role in the breast cancer progression. Aim of the review is to discuss prevalence of mutation in general population and on early stage and various methods of detection of the mutation.

II. THE BIOLOGY OF P53

In 1979, three teams led by A. Levine, P. May, and L. Old discovered the p53 protein, a protein that's highly conserved across animal species, which is encoded by the TP53 gene located on the short arm of chromosome 17 Its sequence, about 20Kb, contains 11 exons, but the first exon does not encode and is located about 10Kb from other exons **[4].** Inactivation of the TP53 gene in human cancer was discovered by Vogelstein's team in 1989 **[5].** The p53 protein consists of 393 amino acids (AA), is divided into regions highly conserved during evolution **[6],** and its role in numerous regulatory mechanisms has been well established. TP53 remains the foremost commonly mutated gene in many human cancers, with mutations (principally, but not exclusively, missense) estimated to occur in 50% of all cancers. Mutant proteins are nearly always defective for sequence-specific DNA binding, thus transacting genes are up-regulated by the wild-type protein **[7]**. Interestingly, the proportion of missense mutations in p53 is above that seen in other tumor suppressor genes, suggesting that expression of p53 mutants may confer a selective advantage over and above loss of wild-type function.

Steady with this theory, numerous human tumor-associated p53 mutants have a number of properties truant from the wild-type protein **[8]**. Other recognized components compromise p53 function to a large extent in cancer missing changes **[9]**.In virus-associated cancers, this may happen by

means of interaction with virally encoded proteins coming about in sequestration or upgraded corruption of p53. MDM2 ties to p53 and advances the ubiquitination of the C-terminus of p53 and ensuing corruption. p14ARF interatomic with MDM2, avoiding affiliation of p53 and MDM2, subsequently stabilizing p53. Debasement of p53 may in this manner be improperly invigorated by overexpression of MDM2 or by erasure or epigenetic hushing of p14ARF. Misfortune of this protein has been detailed in a few common human cancers, especially (but not solely) those in which the p53 quality is wild-type. However, another component of inactivation includes cytoplasmic sequestration of p53 protein, anticipating nuclear localization of the protein and thus inhibiting its activity. (7)

III. FUNCTIONS OF P53

Various studies have appeared p53 to be a transcription factor that targets multitudinous genes and microRNAs in response to cellar stress. The crucial part of p53 as a tumor silencer is to block cell cycle progression and/ or to actuate apoptosis, in response to cellular stresses similar to DNA damage. Impaired p53 exertion promotes the accumulation of DNA damage in cells, which leads to a cancer phenotype. As a transcription factor, p53 forms a differing and complex gene nonsupervisory network. There has been a broad examination to clarify the target sequences that p53 recognizes, the p53 response element (RE), as of late surveyed by Riley et al. [10]. p53 incorporates an exceptionally wide range of biological activities, so this review will center on the part of p53 as an excrescence silencer and its suggestions for cancer treatment.

A. p53 as a Sensor of DNA Damage

p53 as a DNA Damage Sensor: One of the most prominent features of malignant tumours is hereditary instability. There are extremely sophisticated and modern frameworks for detecting DNA damage and repairing the genome. The p53 plays an imperative part. When p53 responds to DNA damage, it evokes either cell cycle capture or apoptosis **[11].** It appeared in 1991 that acceptance of wild-type p53 can initiate apoptosis in leukemia cells **[12].** Mice that have a specific p53 mutant lack the capacity to initiate cell cycle capture, but hold the capacity to actuate apoptosis, permitting them to efficiently suppress oncogene-induced tumors **[13].** In this way recommended that the pro-apoptotic function of p53 may play a more critical role in its antitumor effects than in its acceptance of cell cycle capture.

B. p53 and Apoptosis.

The p53 tumor suppressor limits cellular proliferation by inducing cell cycle arrest and apoptosis in response to cellular stress such as DNA damage, hypoxia and oncogene activation. Many apoptosis related genes that are transcriptionally regulated by p53 have been identified. Numerous reports have described the mechanism by which p53 induces apoptosis. As p53 functions mainly as a transcription factor, it is important to explore the genes regulated by p53 that contribute to the regulation of apoptosis. **[14,15]**

C. p53 and Cell Cycle Arrest:

The p53 protein suppresses tumor arrangement not as it were by actuating apoptosis but moreover by causing cell cycle capture. Depending on the type of cellular stretch, p53 can initiate G1 capture through actuation of transcription of the cyclin-dependent kinase inhibitor p21. This process is well known and has been broadly considered **[16]**. p53 to control the G2/M transition. For instance, p53 can block cell passage into mitosis by the interference of Cdc2. Cdc2 has to bind to cyclinB1 in order to function. Repression of cyclin B1 by p53 also captures cells in G2 **[17]**. However, the transient cell cycle may not lead to tumor destruction, since a cell with oncogenic potential that cannot be repaired may continue multiplication **[18]**. Hence, the other mechanism, cellular senescence, may play a vital role in p53-mediated tumor suppression. Cellular senescence is a changeless cell cycle capture. There are numerous reports with respect to the relationship between p53, tumor improvement, and senescence **[19,20].**

IV. CELL SENESCENCE

Cellular senescence is thought to be important in tumor suppression and contribute to cellular aging **[21]**. The p53 neoplasm suppressor is also an important senescence intermediary, and it appears to be involved in the induction and maintenance of cellular senescence. The first data concerning the importance of p53 on cell senescence was provided by the studies victimization T antigens of SV40 virus that inactivate p53. p53-null fibroblasts stay immortal once propagated in vitro the p53 neoplasm suppressor is also an important senescence intermediary, and it appears to be involved in the induction and maintenance of cellular senescence. Within the context of senescence, p53 is controlled by ATM/ATR and Chk1/Chk2 proteins that cause the posttranslational stabilization of p53 through its phosphorylation **[22].**

A. Angiogenesis.

Pro-angiogenic and anti-angiogenic factors regulate the formation of new blood capillaries (angiogenesis). The p53 super molecule has been shown to limit ontogeny by many mechanisms: (1) officious with central regulators of drive that mediate ontogeny, (2) inhibiting the assembly of 014 The mix of those p53 to efficiently stop working the angiogenic potential of cancer cells **[23]**. Wild-type p53 plays a task in limiting tumor biological processes as incontestable by some clinical studies **[24]**. Mutant p53 plays a central role in promoting ontogeny in carcinoma progression **[25]**, and tumors carrying p53 mutations square measure additional extremely vascularized than tumors harbouring wild-typep53. The loss of TP53appearsto amplifies the HIF (Hypoxia Inducible Factor) pathway. HIF1α has been shown to be physically related to p53 in immuno precipitation experiments. TP 53 promotes MDM2mediated ubiquitination and degradation of HIF-1α, whereas loss of p53 ends up in the HIF response **[26].**

B. TP53 Status and Prognosis in Breast Cancer

Breast cancer could be a heterogeneous illness. Prognosis and the likelihood of a positive response to general therapy are influenced by the type of microscopic anatomy, grade, tumour size, lymphoid tissue involvement, and oestrogen receptor and HER-2 receptor status **[27].** In a worrying half-hour of breast cancers, TP53 is mutated **[28].** There has been a lot of research into the possible links between p53 mutations and breast cancer clinical or pathological options.

The first study to look at gene-expression patterns of carcinoma advised that a minimum of four major molecular categories of carcinoma exist: luminal-like, basal-like, normal-like, and HER-2 positive **[29].** V-J Day of breast tumours are basal-like breast cancers, which are commonly referred to as triple-negative breast cancers (TNBCs). TNBCs, which are identified by the absence of steroid hormone receptor, Lipo-Lutin receptor, and HER2 expression **[30],** are most likely to include all basal-like breast cancers, as well as a few barbiturate breast cancers **[31].** They're also linked to being younger and having a worse prognosis **[32]**. TNBCs had a higher frequency of TP53 mutations **[33].** Recently, it was demonstrated that p53 status was a substantially unfavourable predictive factor for relapse-free survival and overall survival in patients treated with adjuvant anthracycline-containing therapy during a triple-negative cluster. Beneath this treatment, the expression of p53 provides info regarding poor outcomes in triple-negative tumors. **[34]**

In HER2-like cancers, genes linked to ErbB2 amplicon and TP53 mutations are expressed more frequently **[35].** Antibodies against p53 and ErbB2 appear to be more negative prognostic factor **[36]**.Other evidence supports the concept that certain TP53 mutations and ErbB2 overexpression are indicative with doxorubicinin resistance in breast cancer patients **[37]**. Inflammatory breast cancer (IBC) is classified in the TNM classification as the T4d category **[38]**. It's a clinical subtype of locally advanced breast cancer (LABC) with a poor prognosis and aggressive behaviour **[39]**. Inflammatory breast cancer (50 percent) has more TP53 mutations than non-inflammatory breast cancer (20–30 percent) **[40,41]**. The fact that past research exclusively used immunohistochemistry to detect p53 accumulation complicates the interpretation of prognostic findings. ER and PR negative breast cancers with positive immuno-staining for p53 are the most common. This is frequently associated with a high rate of proliferation, a high histological grade, aneuploidy, and a poor prognosis **[42,43]**. In more than 25 studies involving 6000 people, TP53 mutations were found to have a predictive value and the prognostic significance of the TP53 mutation is determined **[44].**

A substantial proportion of people with the Li–Fraumeni cancer susceptibility syndrome, which increases the risk of breast cancer, have p53 mutations in their genes **[45].** This shows that p53 inactivation is important in mammary carcinogenesis, and researchers have studied the structure and expression of p53 in breast cancer intensively. Early research found that mutant p53 was expressed in breast cancer cell lines. Loss of heterozygosity (LOH) in the p53 gene has been found to be a prevalent occurrence in primary breast carcinomas, with mutation of the residual allele occurring in some cases. The remnant p53 allele is mutant in the vast majority of cases of colon carcinomas, but at least 60% of cases with LOH are mutant in breast cancer.

Nonetheless, multiple studies have discovered coding mutations in p53 in breast cancer, and this is now recognised as a common, albeit far from universal, somatic genetic alteration in breast cancer. Indeed, only about 20% of all patients have mutant p53, according to a comprehensive meta-analysis. Several studies have attempted to pinpoint when the p53 mutation develops during breast carcinogenesis. Low-grade ductal carcinoma in situ (DCIS) is largely mutation-free, according to micro dissected tumour material, whereas mutations are more common in high-grade DCIS **[46].**

Despite the fact that the general prevalence of p53 mutation in breast cancer is around 20% **[47]** different kinds of the illness are linked to greater rates. A higher rate of p53 mutations has been found in malignancies emerging in carriers of germ-line BRCA1 and BRCA2 mutations in a number of investigations **[48, 49]**. Furthermore, such carcinomas have a different range of p53 mutations **[50].** Surprisingly, p53 mutation is seen in 100 percent of medullary breast carcinomas **[51]**. This is particularly intriguing because it is now widely acknowledged that medullary breast tumours have clinicopathological similarities to BRCA1-related instances. Indeed, in medullary breast tumours, methylation-dependent suppression of BRCA1 expression is prevalent.

C. The p53 pathway in breast cancers:

In breast tumours, the p53 pathway is disrupted by the absence of p53 mutations. Despite intensive research into the structure of p53, the absolute frequency of mutations in breast cancer is significantly lower than in many other frequent malignancies. What are the molecular processes by which tumours without mutations undermine wild-type p53's tumor-suppressor properties? This question has shed new light on a number of the regulatory pathways that control p53 function. The pathways of p53 inactivation in breast cancer were first discovered in a study of breast tumours with varied p53 mutant status. Only cytoplasmic protein staining was found in a small percentage of patients with wild-type p53 **[52].** As a result, the exclusion of the wild-type protein from the nucleus could be an independent mechanism for p53 deactivation. Following that, researchers discovered changes in both upstream regulatory proteins and downstream p53-induced proteins, suggesting that in breast tumors without mutations, the process may be deactivated or disrupted.

V. PREVALENCE OF MUTATIONS

A. General population

The general population's frequency of germline pathogenic TP53 mutations is unknown, but penetrance figures have been used to estimate it. The statistics range of estimation is from one in 5000 to one in 20,000 **[53, 54]**. Gonzalez and colleagues calculated the prevalence of TP53 germline mutations in the general population by combining the prevalence of specific cancers (breast cancer in women under 30 years of age and adrenocortical carcinoma) in the general population with the frequency of TP53 germline mutations in those cancers. As a result, the frequency was estimated to be between 1 in 17,000 and 1 in 23,000 people. A recent study of germline variation in cancer-susceptibility genes in 681 healthy people found 15 TP53 missense variants but no nonsense or frameshift variants; One missense variant was likely pathogenic, while the others were clinically insignificant mutations.**[55]**

B. Prevalence in early onset breast cancer

The prevalence of TP53 mutations in women with early-onset breast cancer has been studied in several populations **[56, 57].** 5–8% of women diagnosed with breast cancer under the age of 30 who do not have a pathogenic mutation in BRCA1 or BRCA2 will have a pathogenic variant in TP53, according to McCuaig et al. There is very less proportion of women diagnosed with breast cancer aged 30–39 years will have a pathogenic variant in TP53 **[58].** You're more likely to have a TP53 mutation if you have a family history of LFS-related cancers or a personal history of another LFS-related cancer. In a group of patients who had a germline TP53 mutation found owing to having a young start malignancy, it was estimated that 7–20 percent of the mutations were de novo **[59].** De novo mutations are extremely uncommon in hereditary breast and ovarian cancer syndrome caused by BRCA1 or BRCA2 gene abnormalities. Even in the absence of a family history, our finding justifies testing very young onset breast cancer patients for TP53.

C. Prevalence of TP53 mutations in females having breast cancer gene panel testing

According to four recent investigations, the prevalence of TP53 mutations among women who have received panel testing is less than 1%. Among 35,409 women with breast cancer who received testing utilising a panel of 25 cancer genes, Buys et al. discovered 61 women with TP53 mutations (0.17 percent) **[60].** Using a protein truncation test, Moran et al. discovered one TP53 mutation among 190 breast cancer patients with a strong family history and previous negative BRCA1/BRCA2 testing (0.53 percent) **[61].** Kapoor et al. looked at 377 women who were offered gene testing by breast surgeons using multigene panels (5–43 genes, average 14.7) and discovered one TP53 mutation (0.27 percent) among them **[62].** Susswein et al. published the results of over 10,000 cases referred for germline cancer gene testing. They found nine pathogenic and one likely pathogenic TP53 mutation in 3315 women with breast cancer (0.30 percent) who had never had BRCA1/BRCA2 testing, and three pathogenic and one likely pathogenic TP53 mutation in 1894 women with breast cancer (0.21 percent) who had previously had BRCA1/BRCA2 testing **[63].**

D. Detection of p53

Because of its short half-life, p53 protein is undetectable under normal conditions. Mutant proteins, on the other hand, concentrate in the nucleus of tumour cells due to a longer half-life and a different conformational shape. Detection of p53 in the nucleus is highlighted in the vast majority of investigations utilising immuno histo-chemical methods. This technique of detection could result in false positives due to cellular stress-induced stabilisation of wild-type p53 proteins or false negatives due to codon stop, frameshifts, or other destabilising changes. Lack of immuno-staining for p53 despite TP53 gene alterations was identified in tumours with nonsense mutations or deletions/splices **[64],** while other investigations found that immunohistochemistry-based detection of p53 positive did not always indicate a p53 mutation **[65].**

The FASAY test (Functional Analysis of Separated Alleles in Yeast) **[45]** is another approach to detect TP53 status. Reverse transcription by RT-PCR is performed after mRNA extraction from whole blood or tissue (normal or tumoral). The DNA binding domain is amplified using PCR and the PCR product is cloned into yeast using a linearized expression plasmid vector containing the 5 and 3 ends of the TP53 open reading frame. As a result, human TP53 is expressed constitutively in the plasmid. The yeast has an open reading frame (ORF) for adenine that is controlled by TP53 and is regulated by a promoter. The yeasts are grown on a selective medium that is devoid of leucine but rich in adenine. When TP53 is wild-type, the colonies are white and the adenine metabolism is complete. Because mutant TP53 cells do not express adenine, the colonies turn red as a result of the accumulation of an intermediate adenine metabolite. Adenine restricts colony growth; therefore these colonies are smaller than usual. The colour of transfected yeast cells can thus be used to assess the TP53 status **[66].**

TP53 status in breast tumors was studied using a robust and sensitive technique that used three separate methods: p53 immunohistochemistry, FASAY test, and coding sequence sequencing. When more than 15% of the yeast colonies were red, (ii) analysis using the split versions of the test identified the defect in the 5 or 3 parts of the gene, and (iii) sequence analysis from mutant yeast colonies identified an unambiguous genetic defect (mutation, deletion, splicing defects) **[67],** tumours were considered TP53 mutant. FASAY made a significant addition to the investigation by finding many TP53 alterations that were not found by direct sequencing, primarily in samples contaminated with stromal cells **[68,69].**

VI. CONCLUSION

The effects of Tumor Suppressor Protein (TP53) in breast cancer were carefully reviewed in this study. The focus of the review was on the functions of TP53 in relation to breast cancer, as well as numerous clinical applications. Despite recent developments in p53 research showing that

loss of function of the gene causes breast neoplasma, mutations in the gene occur at a substantially lower rate in breast neoplasma than in other solid tumours. The understanding of the upstream pathways regulating p53 activity has greatly improved in recent years, and numerous transcriptional targets for p53 have been identified. These findings have enabled researchers to investigate the molecular mechanisms by which p53 is disabled in breast cancer, in addition to mutations, and have revealed new information about breast neoplasia pathways. In breast cancer, molecular pathological analysis of specific components of the p53 pathway is likely to be diagnostic and prognostic. Furthermore, a number of novel strategies for restoring p53 function in tumours have been proposed **[70].** It will be fascinating to see how these and other novel p53 pathway-targeted therapeutic approaches affect clinical outcomes in breast cancer.

Finally, TP53 status has a significant prognostic impact, which may be useful in determining the best treatment for breast cancer. TP53 mutation is generally linked to a poor response to chemotherapy, hormonotherapy, or radiotherapy. There are conflicting studies on its predictive value, which is linked to the method of detecting TP53 status. We show that the FASAY test and TP53 sequencing are more accurate than immunohistochemistry in determining whether TP53 is mutated. Prospective studies using these two methods could provide a better understanding of its predictive value in terms of treatment response.

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