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Review article

Role and significance of p53 insights into breast cancer progression and therapeutic strategies: A review

Umadevi Bommu, Suneetha Yeguvapalli*

Department of Zoology, Division of Cancer Informatics, Sri Venkateswara University, Tirupati, 517502, Andhra Pradesh, India.

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***Corresponding Author: Suneetha Yeguvapalli,** Department of Zoology, Division of Cancer Informatics, Sri Venkateswara University, Tirupati, India.
Email id: ysuneethareddy4@gmail.com

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Key words: Breast cancer; p53; TP53; loss of heterozygosity; gene expression profiling; therapeutic targets of TP53.

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Abstract

Breast cancer is the most widespread malignancy among women worldwide, with more than one million new cases analyzed every year. The TP53 (p53) gene is mutated in about 20 to 40% of breast cancer cases, contingent upon the size of the tumor and the stage of the disease. This is an early event in the advancement of breast tumors. Several mutations of the TP53 gene have been discovered and their role in the risk of breast cancer and their association with other genetic targets for cancer development has been discussed. The role of the TP53 mutation as a prognostic marker and the role of mutated p53 participation rate in the therapeutic response were discussed. All information available in the examination of TP53 mutations in breast cancer in humans confirms the significant role of TP53 in carcinogenesis of breast cancer. In addition, reviewed therapeutic targets and treatment options discussed may also contribute to the future treatment of breast cancer.

Introduction

In recent days, non-communicable diseases (NCDs) such as Alzheimer's, Parkinson's, cancer, diabetes, cardiovascular diseases, and others are the leading cause of death worldwide. Among them, cancer is found to be a very important peculiar disease and is the leading cause of death for millions in every country [1]. According to data from the World Health Organization (WHO) 2015 estimate, cancer is the first or second leading disease associated with the number of deaths at age 70 in 91 countries, and third or fourth in other countries [2]. According to Globocon estimates in 2018, new cancer data propose to increase the global cancer burden to 18.1 million cases and 9.6 million cancer deaths [3]. Generally, cancer is a class of disease associated with uncontrolled cell proliferation and involves malignant tumors that distort adjacent body parts or tissues by metastasis [4,5]. Studies have shown that cancer is one of the most reliable signs of cancer, including weight loss, abnormal bleeding, changes in bowel movements and chronic cough, etc. Generally, lung, breast, prostate, colorectal, stomach and cervical cancer are the major types of cancer in both males and females [6].

Interestingly, breast cancer is related to various somatic genetic mutations, for example, mutations of oncogenes and tumor suppressor genes [7]. Until this point, the most common genetic mutation destinations are found in the TP53 gene with about 30% of tumors have mutations that usually result in the loss of the wild-type allele (LOH) [8]. An enormous number of studies have assessed the pathogenesis and prognosis of TP53 mutations in breast cancer. Two distinct strategies were utilized to assess TP53 mutations: DNA sequencing and immunohistochemistry (IHC) [9]. The greater part of the TP53 mutations present in breast cancer are point mutations that outcome in the synthesis of stable, dysfunctional and non-degradable proteins that accumulate in tumor cells and can therefore be identified by IHC. The correlation between the accumulation of the

TP53 protein estimated by the IHC and the mutation of the TP53 gene mutation recognized by sequencing is although less than 75% in the breast malignant growth. This is on the grounds that not all mutations provide a stable protein and some mutations cause truncation of the protein and hence cannot be recognized by IHC [10]. Moreover, the role of p53 mutations and their related therapeutic targets in breast cancer have been scanty in previous studies. Subsequently, this review focuses on the investigations of p53 mutation examination in breast cancer and provides significant therapeutic targets [11].

Breast cancer

Breast cancer and its epidemiology

Breast cancer is one of the major causes of cancer deaths faced by women around the world. This is one of the major health problems of the Western world. The breast cancer burden is unevenly distributed, and they exist with a large difference in the morbidity, mortality and survival rates are vary considerably across countries and regions [12]. According to National Cancer Institute (USA) statistics, 2,240 and 2,32,340 new cases in both men and women have been reported respectively in 2013. However, the high number of breast cancer related deaths are reported towards females (39,620) than males (410) [13]. Recent reports indicate an increase in the incidence of breast cancer in low- and middle-income countries. Globocon 2018 estimates that about 11.6% of more than one million new breast cancer cases and 6.6% of breast cancer-related deaths have been reported worldwide [14]. Among 6,26,679 breast cancer deaths around the world in 2018, mostly were occurred in the low- and middle-income countries. Apart from the Asia, Europe and North America countries, Latin America and the Caribbean, Africa and Oceania have also a greater incidence and mortality of breast cancer [15]. In Australia, 2,844 breast cancer cases are estimated in 2014 and also in 2017 approximately 17,730 new cases have been diagnosed. In the U.S. 2,66,120 newly diagnosed invasive breast carcinomas are reported in women in 2018, including 63,960 new invasive breast malignancies [13]. In India, it is common among females in Mumbai, Delhi, Trivandrum, Ahmedabad and Calcutta urban registries and constituting > 30% among all cancers in women. Accordingly, the top 10 countries with the highest rates of breast cancer are shown in Table 1 [16].

Breast cancer classification

Breast cancer is classified according to several classification systems (Figure 1). These can influence the prognosis and affect the response to treatment. The interpretation of breast cancer includes all these factors, such as histopathology, grade, stage, receptor status, DNA-based classification and etc., [17].

Histopathology

The histology of breast cancer indicates a tumors growth pattern. As a heterogeneous disease, breast cancer involves several entities related to unique histological and biological features, clinical manifestations, behavior, and response to treatment. DNA microarray-associated techniques have found many features, such as metastatic propensity and histological degree grade [18]. The most common type of breast cancer is invasive ductal carcinoma, which is not specifically mentioned (IDC-NOS), or of a particular type (IDC-NST), especially adenocarcinoma, which does not have sufficient characteristics to ensure its classification [19]. According to histopathology, breast cancer can be divided into two types: i) common types and ii) rare varieties are as follows.

Some of the common types of breast cancer are as follows

a. Invasive ductal carcinoma (IDC)
b. lnvasive lobular carcinoma (ILC)
c. Medullary breast carcinoma
d. Mucinous carcinoma (MC)
e. Ductal Carcinoma In Situ (DCIS)
f. Metastatic Breast Cancer
g. Inflammatory Breast Cancer (IBC)
h. Triple Negative Breast Cancer

Some of the rare types of breast cancer are as follows

a. Tubular carcinoma
b. Metaplastic breast carcinoma
c. Angiosarcoma of breast
d. Cystosrrcoma phyllodes
e. Papillary breast cancer

Staging of the breast cancer

The TNM system is the widely used and powerful predictor of breast cancer staging. During this process, the staging of the tumor depends on the size of the tumor (T), the fact that the tumor had spread to the axillary lymph nodes (N) and the presence of tumor metastasis (M). Large sizes, lymph node spread and metastases have a greater number of stages and a poor prognosis. A number is added to each letter signifying the size and/or extent of the primary tumor and the extent of cancer spread [20]. The main stages are as follows.

Stage 0 corresponds to pre-cancer status or condition of marker, including ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).

Stages I to III are located in the regional breast or lymph nodes.

Stage IV is a cancerous "metastatic" with poor prognosis because it extends beyond the breast and local lymph nodes.

Stages of breast cancer in detail, cited from [16] (Figure 2).

Stage 0: In this stage, breast cancer means that breast cancer cells have been developed, but they do not spread to surrounding tissues, lymph nodes or other organs.

Stage I: In the first stage of breast cancer, the tumor size is less than 2 cm. It is divided into two stages, stage IA and stage IB.

Stage IA: The tumor measures up to 2 cm, the malignancy does not spread beyond the breast, there are no lymph nodes.

Stage IB: The tumor is 2 cm or smaller, or the tumor does not appear in the breast. A small number of cancer cells are found in the lymph nodes (micrometastases). Each lymph node with cancer cells is no larger than 2 mm.

Stage II: It is classified into two stages; IIA and IIB.

Stages IIA: It is less than 2 cm in size of this tumor. This tumor is no more than 3 the lymph nodes under the arm form metastases that are more than 2 mm in diameter.

Stages IIB: The tumor is smaller than 2 cm but not larger than 5 cm, and small clusters of breast cancer cells are found in the lymph nodes, not larger than 0.2 mm but not larger than 2 mm.

Stage III: It is classified into 3 stages i.e., IIIA, IIIB, and IIIC.

Stage IIIA: This stage indicates tumor size not more than 5cm, the cancer has spread to 4 to 9 lymph nodes in the axilla.

Stage IIIB: During this stage, the tumor starts growing in the chest and skin of your breast, but did not form metastases in the internal organs.

Stages IIIC: At this stage, the cancer effect is 10 or more lymph nodes. If the lower lymph nodes are affected outside the breast, it is also IIIC, but those inside it can expand or become cancerous.

Stage IV: In this stage, breast cancer is spreading beyond the breast and lymph nodes to other areas in the body, such as lungs, distant lymph nodes, skin, bones, liver, or brain.

Table 1. Top 10 countries with the highest incidences of Breast Cancer, cited from [16].

Rank	Country	Age-standardized rate per 100,000 (World)
1	Belgium	111.9
2	Denmark	105.0
3	France	104.5
4	The Netherlands	99.0
5	The Bahamas	98.9
6	Iceland	96.3
7	United Kingdom	95.0
8	Barbados	94.7
9	United States of America	92.9
10	Ireland	92.3

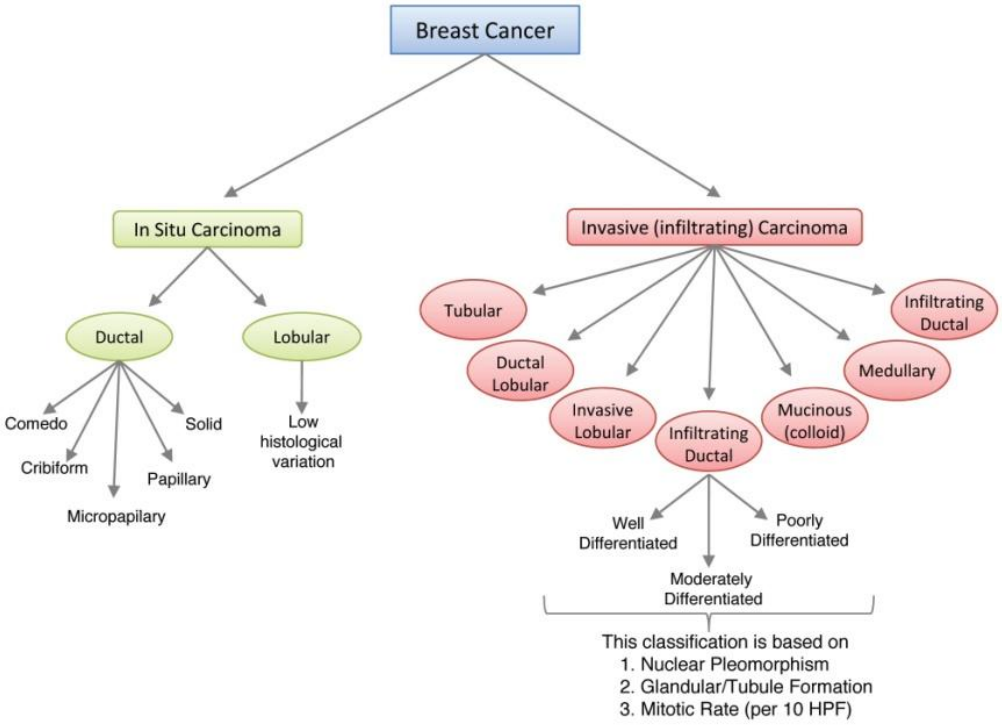


Figure 1. Histological classification of breast cancer subtypes, cited from [59].

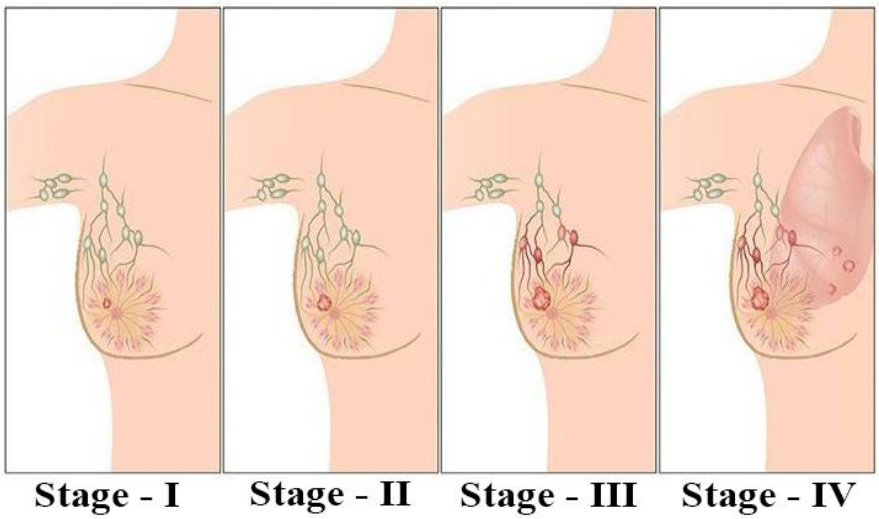


Figure 2. Stages of breast cancer.

Receptor status

Usually, breast cancer cells comprise of various receptors on the surface, as well as in the cytoplasm and nucleus. It should be noted that breast cancer cells may or may not have three significant receptors: the estrogen receptor (ER), the progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2). The development of ER+ cancer cells (i.e., cancer cells containing estrogen receptors) is estrogen-dependent and can therefore be treated with a drug that prevents estrogen effects (e.g., tamoxifen) and commonly has an excellent prognosis [21]. Untreated HER2+ breast malignant growth is typically more destructive than HER2- breast cancer, however HER2+ cancer cells react to drugs include the trastuzumab monoclonal antibody (combined with conventional chemotherapy), which enormously improves the prognosis. Cells lacking these three types of receptors (such as ER, PR or HER2) are called triple-negative cells, despite the fact that they typically express receptors for other hormones, such as androgen and prolactin receptors. In addition to these hormone receptors, Ki67 (also known as MKI67) and p53 key breast cancer molecules have been reported in previous studies [22].

DNA-based classification

Various DNA tests include DNA microarrays, have contrasted normal cells to breast cancer cells. Specific changes in specific breast cancers can categorize cancer in different ways and may help to choose the most effective treatment for that marker type [23].

Gene expression profiling of breast cancer

The combination of traditional pathology with genetic characterization and functional genetics will increase our understanding of the genetic basis of breast cancer. Gene expression profiling techniques can better predict clinical outcomes compared to traditional clinical and pathological parameters [24]. It can help clinicians objectively assess local treatment outcomes and evaluate all the benefits of systemic endocrine support therapy and chemotherapy. The gene expression profile has grouped breast cancer into four different subtypes: the basal-like subtype that is negative for the estrogen receptor (ER-negative) and negative for HER2 (HER2-negative); the HER2 subtype, is described by expanded expression of HER2 and gene mapping on the HER2 amplicon; and two luminal ER-positive subtypes: luminant A is portrayed by elevated levels of ER and genes related with it, whereas luminant B is portrayed by low levels of ER and high articulation of the genes associated with the proliferation process [25, 26].

Microarray expression analysis is a high-throughput technology for molecular biology that provides simultaneous access to the gene expression profiles of thousands of genes [27]. Gene expression models based on a microarray can be used to understand the etiology of underlying diseases such as breast cancer [28]. Types of genetic damage, such as gene deletions, point mutations (p53 mutations), and gene amplification, have been implicated in the development of basal type breast cancer [29]. Microarray-based gene expression analysis can be used to systematically analyze, demonstrate, and classify molecular diversity and determine the role of genetic mutations in modifying the expression of oncogene and tumor suppressor gene expression, as well as in the development and progression of the underlying breast cancer. There are three methods of using DNA microarray in cancer biology: i) class comparison, ii) class prediction, iii) class discovery [30]. The class comparison is used to identify differentially expressed genes (DEGs) in the different types of cells of tissues from different experimental conditions in different patients or cells [31]. This involves the identification of differentially expressed genes between tumor tissue of a patient who responds to a given treatment and a patient

who does not respond to treatment. The class prediction is used as like class comparison problems, the classes are independent of the expression data [27]. This involves identifying genes that are differentially expressed between a patient who responds to a given treatment and a patient who does not respond to treatment (for example, a population test). Particularly useful in clinical options for treatment selection or diagnostic classification or prediction of prognosis. Finally, class discovery is very different from class comparison or class evaluation [32]. Its classification is not independent of the definition of the expression profile. The goal is to find a subset of cases (groups) revealed by gene expression profiles and to identify the genes that distinguish clusters [33]. Accordingly, previous studies have shown that six genes, such as, BRCA1, BRCA2, TP53, PTEN, STK11 and CDH1 with 51 variants of the 40 genes strongly associated with breast cancer risk [34]. Among those, the destruction of the p53 pathway is one of the most common genetic mutations in breast cancer and plays an important role in cell cycle regulation, apoptosis and DNA repair [35]. TP53 mutations are associated with cancer prognosis and, according to the International Agency for Research on Cancer (IARC), about 23% of breast cancers have TP53 mutations. TP53 mutations are usually point mutations that result in the replacement of a single amino acid in the p53 protein. Altogether, therefore in this review, we further reported the importance and pathophysiological role of p53 in breast cancer [9, 36].

Biology and role of p53 in cancer

The p53 is the most conserved protein and is encoded by the tumor suppressor gene, i.e., TP53 situated on the short arm of chromosome 17p13. Since its revelation, impressive advancement has been made in understanding the functioning and regulation of this protein [37, 38]. The p53 protein contains 393 amino acids and is broken down into well-conserved regions during evolution. The protein is comprised of three functionally distinct regions, (i) the N-terminal region (amino acids from 1 to 42 (AA1-42)), (ii) a proline-rich domain associated with the induction of apoptosis (AA63-97), (iii) a binding domain of DNA located in the core region of the protein (AA102-292), a tetramerization domain (AA323–356), and (v) a C-terminal region (AA363–393). This C-terminal zone involved in the tetramerization and the regulation of p53 function and/or activity [39, 40]. In addition, there are nuclear localization sequences at the C-terminal end (NLS, nuclear localization signal) for export to the cytoplasm at the N- and C-terminal ends (NES, nuclear export signal), supported for the subcellular localization regulation of p53 (Figure 3).

The p53 tumor suppressor is a multifunctional protein that regulates cellular stress responses such as cell cycle arrest, apoptosis and aging. In healthy cells, prolonged proteasome depletion maintains low levels of p53, but during cell stress incorporates over expression of oncogenes or DNA damage, the p53 expression levels are expanded, which results in diminished degradation rather than enhanced transcription or translation that allows for the enhanced cellular stress responses mediated by p53 [41]. Therefore, this is evident that inactivation of p53 by mutation or dysregulation is generally observed in human cancers. p53 was available in 50% of human cancers and the other half of tumors appeared to have defects in the p53 pathway [35].

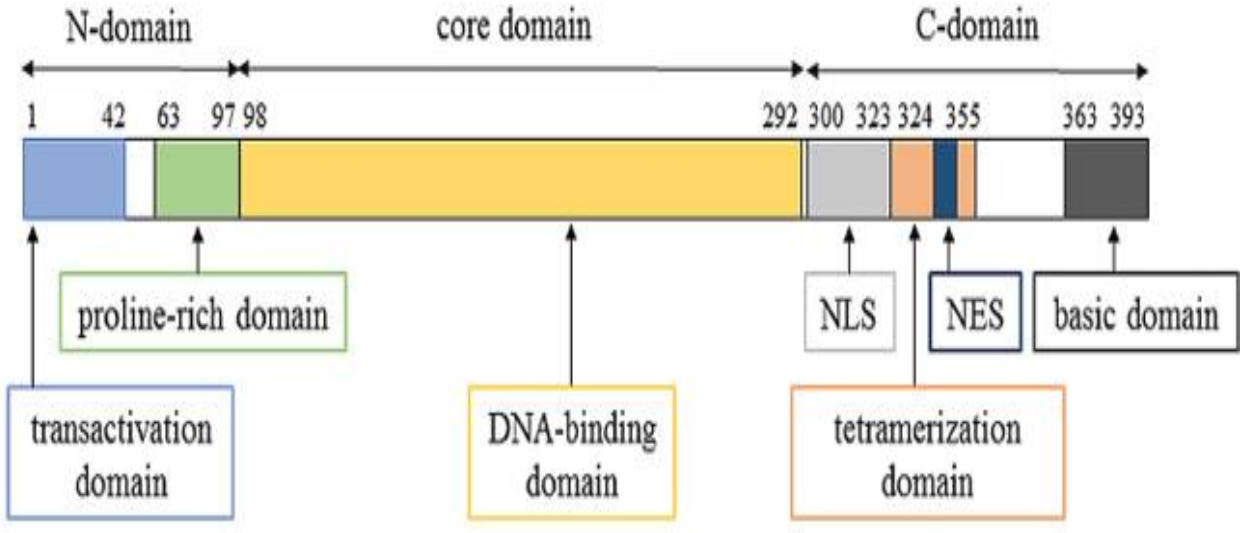


Figure 3: The p53 protein structure, cited from [51].

TP53 signaling pathway

For the most part, a considerable lot of stress signals such as oxidative stress, DNA damage by chemical mutagens and activated oncogenes can be activated p53 signaling cascade. Tumor protein p53 is provided as a transcription factor for p53–controlled gene activation, which recommended that, three major outcomes incorporate programmed cell death, arrest of the cell cycle or cellular senescence [46, 47]. Other P53 controlled gene functions can be interfaced with adjacent cells, repair damaged DNA or improve or enhance the functions of p53 protein, and integrate these weight reactions with other signaling pathway. Deactivating mutation in TP53 is the most common well–known approach to influence a specific gene in cancers [48, 49]. Some of TP53 mutations confer "function gain", and signifying that the mutated TP53 protein, is really adding to various phases of tumorigenesis or drug resistance. Over expression of MDM2 eliminates the ability of p53 to cause cell cycle arrest and apoptosis. In approximately 30% of human osteogenic sarcomas and soft tissue sarcomas, MDM2 is overexpressed due to gene amplification, which suggests its role in the occurrence of these tumors.

TP53 mutations and their significance in breast cancer

The TP53 mutation is the most well-known genetic alteration in breast cancer, and the function of p53 is impeded in 50% of cancers. More than 90% of the p53 gene mutations were found in the DNA binding domain, but examination of the entire TP53 coding sequence began to reveal an increase in the N and C terminal mutations of the protein. The mutant TP53 can subsequently be a therapeutic target [8, 9]. Molecular target drugs usually act by hindering oncogenes that overexpress in cancer cells, which are therapeutic targets. Regarding TP53-targeted therapy, therefore, wild-type and mutant TP53 gene-targeted therapies have been proposed [50].

More than half of the cancer cases reported mutations in the TP53 gene, with a recurrence of around 20% to 30%. The TP53 mutation is thought to be an early event in the improvement of breast cancer and is associated with poor prognosis and drug resistance [51]. The TP53 mutation in most human cancers is a missense substitution brought about by a single nucleotide substitution group in the DNA binding domain of the protein. As indicated by the IARC TP53 database (www.p53.iarc.fr), ~70% of breast malignant growth mutations in TP53 are missense [9]. There is evidence that the high recurrence of p53 is significantly impaired in breast cancer because of carriers of BRCA1 and BRCA2 germline mutations. TP53 mutations are provided to anticipate breast cancer resistance to anthracyclines, doxorubicin and 5-fluorouracil/mitomycin, and mutations explicitly influencing L2 and L3 cyclic structures are associated with an absence of response to chemotherapy [52]. The status of the TP53 mutation and gene expression profiles are groundbreaking diagnostic markers for breast cancer. TP53 mutations are related to an expanded risk of allelic imbalance and heterozygosity in hereditary and sporadic breast cancers [53]. In breast cancer, p53 mutations can indicate DNA damage that lead to hindrance of apoptosis, induction of genetic instability, bypass of senescence, inhibition of autophagy at the beginning of tumor development, regulation of lipid metabolism, sustaining proliferative signaling, induction of angiogenesis, promotion of epithelial to mesenchymal transition, regulation of inflammatory processes in tumor growth and development, induction of migration and invasiveness, promotion of sternness in metastasis [54].

Therapeutic targets for TP53 in breast cancer

P53 assumes a key role in suppressing tumors, essentially by growth arrest, inhibiting apoptosis, aging, angiogenesis and restricting the sensitivity of cancer cells to chemoradiation, making it a target interesting for the discovery and development of drugs. This could be a novel and powerful therapeutic target in triple-negative breast cancer [55]. Down regulation of the TP53 gene makes the cells containing damaged DNA more likely to survive and differentiate. In the event that p53 synthetic malignant drugs are identified and developed, (i) cancer treatment requires p53 cancer cells containing mutations, and (ii) in the early stages of cancer treatment, chemoprevention is required to remove cancer-infected cells containing the mutated p53 [56]. In addition, since typical cells do not carry a p53 mutation, the adverse effects of the fatal drug synthesis of p53 should be less. Consequently, p53 can likewise influence the metastatic conduct. P53-dependent therapy may provide other therapeutic advantages [57]. There are at present some exploratory techniques for p53 that can be utilized to treat malignancy: i) the re-expression of wild-type p53 (WT) in a tumor cell, i.e., gene therapy (retrovirus containing TP53, TP53 containing adenovirus: Ad5CMV-p53) to transform WT-TP53; Ii) disrupt the cells deficient in WT-p53 (altered adenovirus: ONYX-015); Iii) pharmacological initiation (restraint of binding to p53/mdm-2: superTIP, nutlins, and direct actuation: polyamines, reactivation of WT-p53 activity in mutant cells: PRIMA-1); and iv) stabilization of the unstable mutant p53 structure utilizing a compound and/or small molecules that advances the native conformation of p53 [50, 58].

Conclusions

All data available in the analysis of TP53 mutations in breast cancer in humans confirm the important role of TP53 in carcinogenesis of breast cancer. Although only a small percentage of breast tumors have TP53 mutations, data accumulation in recent years suggests that TP53

activity is inactivated by modification of the TP53 pathway targets in a large number of breast tumors. Several other mechanisms of inactivation of TP53 have been described, including several TP53 binding proteins (e.g., MDM2), mutations in genes encoding the proteins responsible for phosphorylation, acetylation and ribonucleoside (e.g., ATM and CHK2), the gene encoding the transcription factors related to TP53 (e.g., HoxA5), alterations in tumor suppressor genes (e.g., BRCA1 and BRCA2). These results provide the basis for a high-throughput genomic analysis that simultaneously analyzes all TP53 pathway genes and provides new information on its role in breast tumorigenesis. Molecular physiopathological analysis of specific components of the TP53 pathway can have profound effects on the diagnosis, prognosis and optimal treatment options for breast cancer patients. In addition, described therapeutic targets and ways, such as re-expression of WT-p53, disrupt the cells abnormalities in WT-p53, pharmacological activity and structural optimization of mutated p53 using small molecule targets may also contribute to the future treatment of breast cancer.

Conflict of interest

All authors declare that no conflict of interest.

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