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Mutant Status of the P-53 Gene as An Unfavorable Marker in Breast Cancer

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Abstract

Breast cancer affects more than one million patients annually in the world and is a leading cause of mortality. Histological type, grade, tumor size, lymph node involvement, and estrogen receptor and HER-2 receptor status, all influence prognosis and the probability of response to systemic therapies.

Purpose: The aim of this current review is to emphasize possible links between alterations of the P-53 gene together with its protein in pathological features of breast cancer.

Method: New means were being investigated to promote a stronger anti-oncogene response, using both RNA-based p53 vaccines and the likelihood of response to specific oncological therapies.

Results: Genetics studies shown that mutant p53 status was a strongly unfavorable prognostic factor for relapse-free survival and overall survival only in a triple negative group in patients treated with adjuvant anthracycline-containing chemotherapy. The adjuvanted vaccine induced the type T I cells helper response in most patients. However, the response has not yet been shown to be strong enough to be beneficial as monotherapy and most patients have had T-helper cells that have failed to produce effective cytokines to kill cancer cells. The results of these studies provided a justification for attempts to discover and apply new vaccines to cancer patients using p53-derived peptides.

Conclusions: Recent studies have shown that the condition of the mutant P-53 gene was an unfavorable prognostic factor for the survival of patients without relapses in BC in the group with triple negative forms of BC in patients treated with adjuvant chemotherapy

Keywords: ***Inflammatory breast cancer; Triple-negative breast cancers; P-53 gene; MDM2-p53 complex***

1. Overview

Breast cancer affects over one million patients annually in the world with a prognosis dependent on clinical and biological factors, such as age, tumor size, nodal status and histological grades. Depending on the evolution of the tumor, treatments

combine primary tumor surgery with the breast radiation therapy, chemotherapy or hormone therapy. Breast cancer is a heterogeneous disease and the tumor size, lymph node damage and estrogen receptor and HER-2 receptor status, all influence the prognosis and likelihood of response to cancer therapies [1].

2. Objective

Breast cancer (BC) is the leading cause of cancer mortality in women worldwide. The aim of this current review is to emphasize possible links between alterations of the P-53 gene together with its protein in pathological features of breast cancer.

3. Method

New means were being investigated to promote a stronger anti-oncogene response, using both RNA-based p53 vaccines and the likelihood of response to specific oncological therapies. A large number of oncological studies have confirmed that microRNA-type nucleic acid (miRNAs) has an important role in the development and progression of BC. MicroRNA-214 (miR-214), a member of the miRNA family, has been shown to function both as a tumor suppressor and as an oncogene in various types of human cancer depending on the interaction with other types of RNA chains or cytoplasmic intracellular molecules. It was also stated that the P-53 mutant gene, through its p-5e isomorphic protein, was the target gene of miR-214 promoting cancer progression.

4. Results

The P-53 gene is mutated in approximately 30% of breast cancers. Possible links between P-53 gene status, wild or mutant, present on chromosome 17 or absence and the clinical or pathological features of breast tumors, have been frequently investigated, FIG. 1.

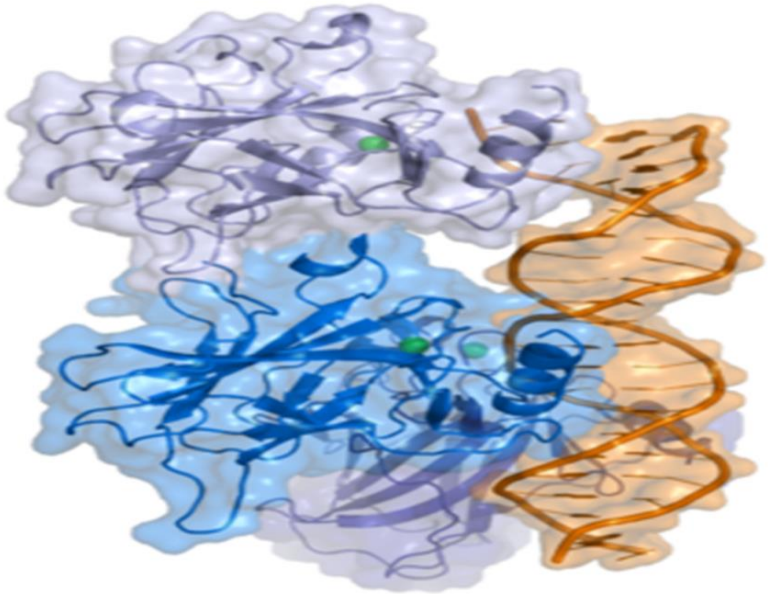

FIG. 1. **P-53 Protein in Active Tetrameric Form.**

Genetic studies that have examined breast cancer gene expression patterns have suggested that there are four major molecular classes of breast cancer: luminal-like, basal-like, normal-like, and HER-2 positive [2]. In a group with triple-negative breast cancer in patients treated with adjuvant chemotherapy, it was found that the condition of the P53 gene was an unfavorable prognostic factor for relapse-free survival and overall survival of those patients [3].

P-53 gene mutations are more common in inflammatory breast cancer (50%) than non-inflammatory breast cancer (20-30%). The interpretation of prognostic data was initially complicated by the fact that the studies in previous years used only immunohistochemistry to detect the accumulation of p53 proteins in malignant cytoplasmic cells as opposed to recent studies based on molecular or genetic analyzes performed by the by immune-enzymatic or molecular methods as Elisa, Sequential Gene Method (SGN), Reverse transcription polymerase chain reaction, (RT- PCR) assays and CRISPR technology.

Breast tumors with mutant or absent positive immuno-fluorescent genes are usually estrogen receptor (ER) and progesterone receptor (PR) negative. These types are often associated with a high percentage of proliferation, a high histological degree, aneuploidy, and an unfavorable prognosis [4].

Genetic expression of breast cancer is characterized by four major molecular classes of breast cancer: luminal-like, basal-like, normal-like, and HER-2 positive. Basal type breast cancer accounts for 15% of breast cancers and is very aggressive being described as a form of triple-negative cancer (TNBC). TNBCs are characterized by lack of expression of estrogen receptors, progesterone receptors and HER2 and include both basal breast cancers and some types of poorly differentiated luminal breast cancer.

It is known that the carriers of the germline P-53 gene mutation, which are part of the Li-Fraumeni family syndrome, have an onset of breast cancer at a young age. P53 germline mutations are found in hereditary cancers and may also be associated with BRCA1 and BRCA2 gene mutations negative in breast cancer [5].

The level of p-53 protein among the sera of the studied groups has been measured in U/ml using the ELISA technique. The patients' age range was 22-84 years (mean 51.29) most of them were in the fourth decade. 21 patients (42%) were premenopausal and (58%) were pos-menopausal. The study showed the demographical features which indicated that the mean of age of the majority of patients was within or above the menopause duration (51.29 ± 12.18 years) with the highly significant difference in comparison with control (29.42±10.21years), this result is comparable to some extent with the previous study (50.9+11.8) (Haider, 92010). The mean of TP53 of malignant cases was 47±33.5 U/ml in comparison with 27.9±12.7 U/ml for healthy control [6].

In many studies the function of the P-53 gene was altered in nearly 50% of cancers and p53 was inactivated by mutations in the DNA binding domain or deletion of the carboxy-terminal domain. It has been shown that some missense mutations gain oncogenic properties [7]. As the best method to test the normal functionality of p-53 protein was used the microbiological Fassay test, FIG. 2.

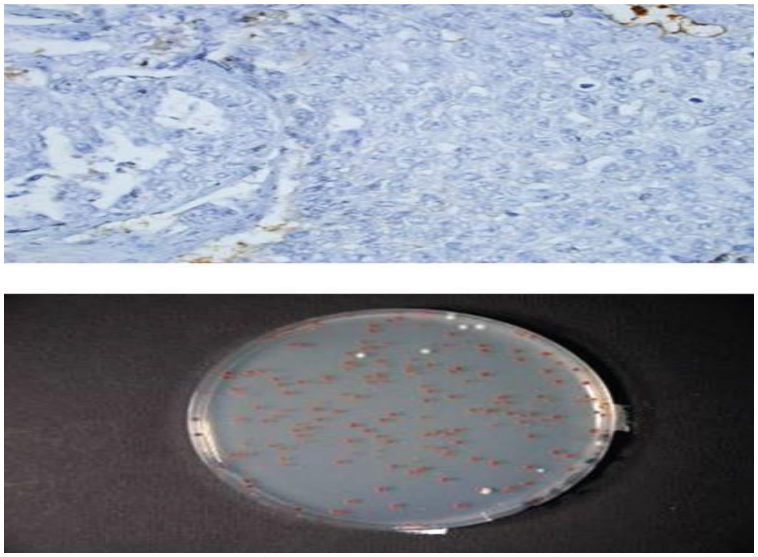

FIG. 2. **Fassay Test, Detection of P53 By Immune-Cytochemistry and Determination of Tp53.**

Detection of p53 by immune-histo-chemistry cannot determine P-53 gene function status but only the presence or absence of p-53 in normal or malignant cells [8]. With the recent discovery of specific MDM2 inhibitors that activate p53, it is now possible to probe the p53–MDM2 response in different tumor settings. [9]. However, intrinsic DNA damage in tumor cells may result in elevated levels of post-translationally modified p53 (for example phosphorylation at Serine-46 and Serine-392). Further stabilization of modified forms of p53 by nutlin-3, which inhibits the negative autoregulatory loop between MDM2 and p53, results in the activation of other p53-dependent pro-apoptotic pathways [10], FIG. 3

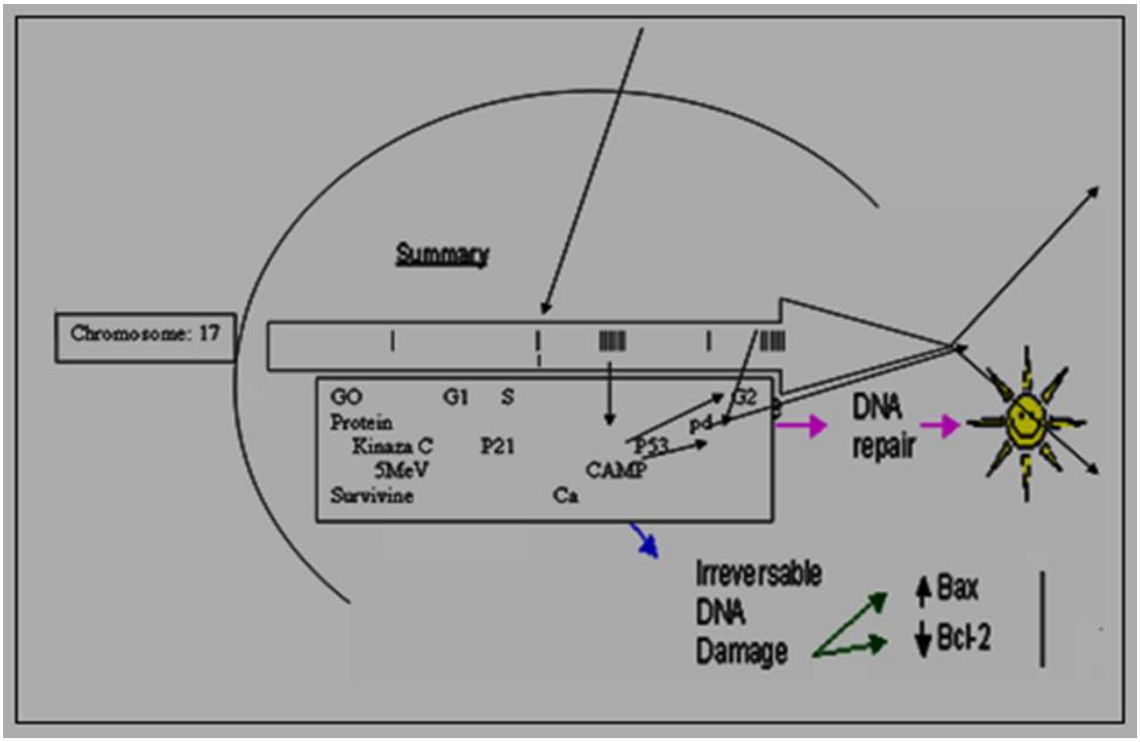

FIG. 3. P-**53 Protein in Interaction by Enhancing of the Apoptotic Signals for DNA Repair.**

5. Discussions

With the help of reporter vectors labeled with the enzyme luciferase, it has been shown that the P-53 gene can be the target of a micro-RNA classified as miRNA-214. Transfection with miR-214 in breast cancer (BC) cancer cells found that miRNA overexpression-214 significantly increased cell invasion by decreasing P-53 gene expression. By contrast, overexpression of the P-53 gene blocked the effects of miR-214. In conclusion, this study demonstrated that this type of miRNA-214 functions as an oncogene in BC, at least in part by promoting cell invasion due to loss of expression of the P-53 gene [11].

Antibodies specific for the p53 isoform protein have been used in some clinical trials using p53-derived peptides to look for evidence of an immune response in cancer patients with the mutant P-53 gene. Although it has been shown that cancer patients produce antibodies against the cancer protective protein, p53, the frequency and extent of this response have not yet been finalized. Although a large number of BC patients produce p53 reactive T cells, short-term in vitro stimulation with p53-transfected dendritic cells revealed that although more than 40% of breast cancer patients have CD4 and CD8 reactive T cells. p53 in their peripheral blood, favorable responses occur most frequently in patients with high expression of p53 proteins in their tumors, [12,13].

The results of these studies have served as justification for attempts to vaccinate patients using p53-derived peptides, and many clinical trials are ongoing. The vaccine was administered under adjuvant conditions and induced the type I helper response in most patients. However, the response was not strong enough to result in clinical benefits as monotherapy, as most patients who had stimulated T-helper cells failed to produce destructive cytokines from cancerous tumors, indicating that these T responses -P53 specific helpers are not efficient enough. Therefore, research will continue to promote a stronger anti-cancer response, using both p53 peptide vaccines and tumor RNA reactivated dendritic cell vaccines. [14].

Many studies suggested that P-53 gene status may influence response to antihormonal treatments. TP53 mutations are less frequent in patients with ER-positive breast cancers, but they are associated with a poorer prognostic in these patients. In vitro studies on human breast cancer cell lines with gene P-53 wild (WT) or P-53 mutant were shown that BC with P-53 mutated cells were more resistant to cytotoxic effects of 4-hydroxy-tamoxifen compared to p53 wild-type cells. Clinical trials in patients with locally advanced breast cancer treated with tamoxifen or primary chemotherapy have shown that the presence of P-53 gene mutations is associated with lower survival. Temporal activation of the non-mutant P-53 gene present in a form of BC with a specific inhibitor of the MDM2 protein led to complete inhibition of tumor growth [15].

6. Limitations

The condition of the P-53 gene has shown a strong impact on the prognosis, and this could be useful in choosing the best treatment for breast cancer. In general, the P-53 gene mutation was associated with a poor response to chemotherapy, hormone therapy, or radiation therapy, and the FASAY test and TP53 sequencing proved better than immunohistochemistry to determine the status of the mutant or non-mutant P-53 gene.

7. Immune treatment

In many laboratory studies, today are ongoing clinical trials with anti-CTLA-4 and immunological control points, ie. PD-1 / PDL1 can improve the prospects of patients with various malignancies [16]. Interactions between PD-1 and its ligands, PD-L1 and PD-L2, are complex and occur in several stages of an immune response. Also, there is an activation mechanism in the lymph node where PD-L1 / PD-L2 on an antigen-presenting cell (dendritic cell) negatively regulates T-cell activity by PD-1 and an interaction between B7 and PD- L1. The PD-1 pathway is also likely to be important in the tumor micro medium where PD-L1 expressed by tumors interact with PD-1 on T cells to suppress the effector function of T, FIG. 4.

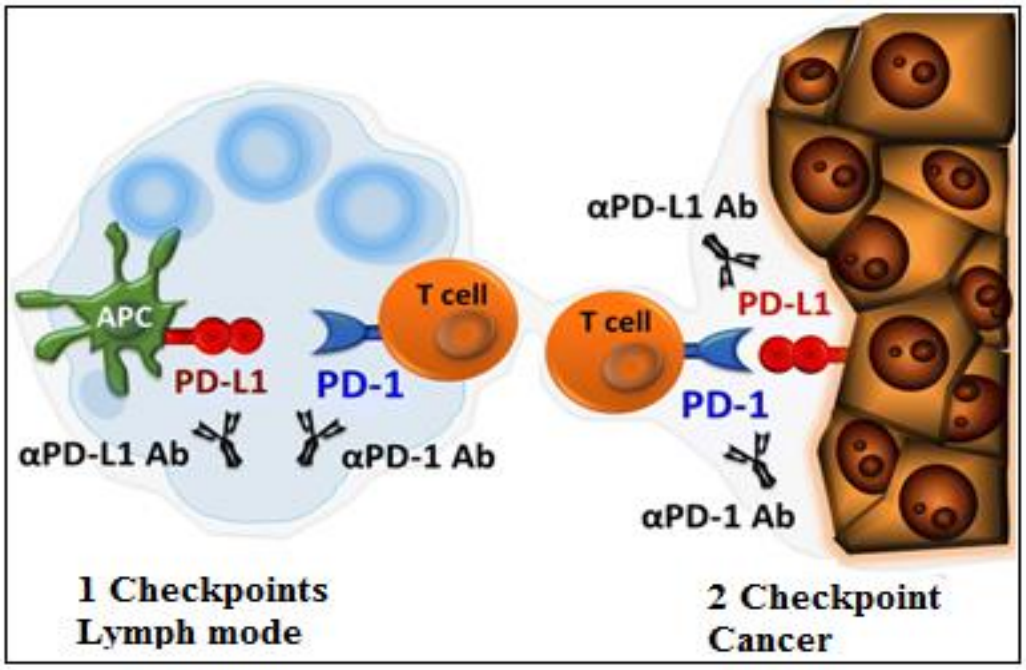

FIG. 4. **Pd-1 Inhibits T-Cell Responses by Interfering with The T Cell Receptor Signaling Unlike Competing Out-Cd28.**

It is important to remember that the breast cancer survival rates are, in reality, going to be higher. This is because the breast cancer survival rates data is gathered from many people with the disease over 5 years. Thus, with the ongoing improvements and advancements in breast cancer screening, research, early detection and advanced tailored treatment, the outcomes at present will be even better than in past years. Also, it is important to bear in mind other factors discussed in this post, such as stage, grade, and hormone receptor status play an important role in prognosis.

8. Conclusion

The special laboratory techniques used to identify the genetic make-up of cancers, this genetic information may become a better predictor of cancer aggressiveness and outcome than the stage, which has been the diagnostic indicator of choice in the past. Additionally, this genetic information will likely play an increasing role in directing treatment. Prospective studies using these two methods could better determine its predictive value according to response to treatments.

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