Mutant Status of the P-53 Gene in Relation with microRNA, as an Unfavorable Marker in Breast Cancer, a Systematic Review

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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: Aim of this work was to emphasize possible links between alterations of the P-53 gene, together with its protein, in the pathological features of breast cancer, resistant to a conventional therapy.

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

Results: Studies have shown that mutant P-53 gene had 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 T1 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 justified attempts to discover and apply the new vaccines to cancer patients using p53-derived peptides.

Conclusions: Conditions of the mutant P-53 gene or deletion of 17p chromosome were an unfavorable prognostic factor for the survival of patients, treated with adjuvant chemotherapy, in the groups with triple-negative forms of BC.

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1. OVERVIEW

Breast cancer (BC) is the leading cause of cancer mortality in women worldwide. BC 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 breast radiation therapy, chemotherapy or hormone therapy. BC 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.

Along the past decade, several genes have been identified as genetically related to breast cancer inheritance. BRCA1 and BRCA2 are considered the most important genes related to inheritance predisposition of breast cancer, along with PTEN and TP53 genes. The susceptibility of breast cancer for patients with the BRCA1 mutation is up to 87% for older women. Another gene, TP53, codes for a protein that acts as the guardian of the genome, binds to DNA in order to perform transcriptional regulatory functions, regulation of the cell cycle and apoptosis among other functions. According to genetic counseling and epidemiologic studies, the risk of developing cancer for patients with TP53 polymorphisms is 90%.

2. OBJECTIVE

This review has aim to emphasize possible links between alterations of the P-53 gene by mutant status or deletion of chromosome 17p, together with its isoform protein p-53, in pathological features of breast cancer with the unfavorable conventional oncologic treatment.

3. METHODS

New methods were investigated to promote a stronger anti-oncogene response using both RNA-based p53 vaccines and the likelihood of response to specific oncological therapies. In this study were analyzed a number of oncological studies which confirmed that some type of 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 in wild type and as an oncogene in mutant status, in various types of human cancer depending on the interaction with other types of miRNA chains or cytoplasmic intracellular molecules, [1].

The anticancer properties of the nanoplatform vaccine were due to the inhibition of rRNA transcription and activation of pro-death autophagy [2]. A better

understanding of the stress pathways as nucleolar and endoplasmic reticulum stress and autophagy could open novel avenues for investigating specific and effective pharmacologic targets for new drug development and therapeutic approaches in processes of death autophagy, [3, 4].

MicroRNAs is an evolutionarily conserved non-coding RNAs that contain 19–25 nucleotides and arise by cleavage from 70 to 100 nucleotide hairpin precursors, [5]. MicroRNAs, (miRNAs,) have had provided a new dimension to our understanding of complex gene regulatory networks. This can function as oncogenes or as tumor suppressor genes, although these data are yet limited. Also, it is known that some type of microRNA(miRNA), suppressed, like the micro ARN, miR-15a/16-1 cluster from 13q14-minimal region chromosome, (MDR), causes development of indolent B cell-autonomous, clonal lympho-proliferative disorders observed in human hematological diseases, [6].

Numerous studies have demonstrated that aberrant expressions of microRNAs are involved in cancer initiation and development. Furthermore, p53, which has been reported to be downregulated past 50% in different cancer diseases, was predicted to be the target gene of miR-214 using bioinformatics software programs. Moreover, luciferase reporter vectors were constructed and it was confirmed that p53 is a target of miR-214. Following the transfection of miR-214 into in cancer diseases, particularly breast cancer (BC) cells, were found that the overexpression of miR-214 markedly enhanced cell invasion through the downregulation of p53 expression. By contrast, the overexpression of p53 abrogated the effects of miR-214. In conclusion, this study demonstrates that miR-214 functions as an oncogene, at least partly by promoting cell invasion through the downregulation of p53, [7].

Moreover, their localization, together with the levels of miRNAs and target mRNAs, and the affinity of the miRNA-mRNA interaction, are important for gene regulation. It is not known the relation which can be between a microRNA (miRNA and messenger RNA (mRNA) in the cytoplasmic cellular stress but is expected a negative correlation between expression levels of these putative target mRNAs and the corresponding miRNAs, [8].

Malignant transformation is characterized by dysregulation of diverse cellular processes that have been the subject of detailed genetic, biochemical, and structural studies, but only recently has evidence emerged that many of these processes occur in the context of biomolecular condensates of RNA molecules with related functions.

RNA molecules play regulatory roles in diverse biomolecular condensates, including the nucleolus, transcriptional condensates, co-transcriptional splicing condensates, nuclear speckles, paraspeckles, and stress granules. Localization of nuclear condensates can be mediated by proteins that bind to specific DNA

or RNA sequences and cytoplasmic condensates can form at sites on the plasma membrane and regulation of condensates can occur at many levels, for example, posttranslational modifications (PTMs) of molecules or the presence of RNA may change the properties that influence formation. Insights into dysregulated metabolic processes and cancer, [9]. Also, was discovered that the P-53 mutant gene, through its p-53 isomorphous protein, is the target gene of miR-214, promoting cancer progression [10].

4. RESULTS

In medical specialty literature was described that the P-53 gene is mutated in approximately 80% of triple-negative cancer (TNBC). Possible links between P-53 gene status, wild or mutant, present on chromosome 17 or absence and the clinical or pathological features of breast tumor, have been frequently investigated. Many studies shown that the function of the P-53 gene was altered in nearly 50% of cancers disease by mutations in the DNA binding domain or deletion of the carboxy-terminal domain. It has been demonstrated that some missense mutations gain oncogenic properties.

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. 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 of those patients or relapse-free survival, [11].

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.

The product of P-53 gene, p53 protein, is a phosphoprotein which is made up of 393 amino acids and comprises four units of which one domain activates transcription factors. The other domain is responsible for recognizing specific DNA sequences which is called as core domain. The other two domains are responsible for tetramerization of protein and recognize damaged DNA (such as misaligned base pairs or single-stranded DNA, **Figure 1**.

Figure 1 P-53 protein in active tetrameric form. (It is found out that amino-acids Arg175, Gly245, Arg248, Arg249, Arg273, and Arg282 are mutation hot spots which are present in various human cancers in central core domain). [Scheme from Toufekhtchan E, Toledo F. (2018). The Guardian of the Genome Revisited: P53 Downregulates Genes Required for Telomere Maintenance, DNA Repair, and Centromere Structure". *Cancers*. 10 (5): 135].

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 [12].

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 a 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 [13].

The level of p-53 protein among the sera of the international 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 postmenopausal. 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 ± 10.21 years), 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 [14].

In last years, as the best method to test the normal functionality of p-53 protein was used the microbiological Fassay test with the detection of p-53 by immune-hysto-chemistry and determination of P-53 gene activity, **Figure 2**, [15].

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 [16, 17].

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

Figure 2 Detection of p53 by immune-cytochemistry and determination of P-53 activity, (Fassay test). [From Varna M et al. TP53 Status and Response to Treatment in Breast Cancers. *J Biomed Biotechnol*, [15].

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, [18, 19].

DISCUSSIONS

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 [20].

Figure 3 Immune Checkpoint Blockade in Cancer Therapy by the pathway of programmed cell death (PD) and Cytotoxic T lymphocyte. There are at least two interacting molecules in the PD pathway: PD-L1 -PD-1, which leads to activation of T-cell in Checkpoints lymph mode and PD-L1-PD-1 which induces suppression tumor in Checkpoint Cancer. Antibodies anti PD-L1 and anti PD-1 stop all process. (Ghosh C et al. A snapshot of the PD-1/PD-L1 pathway. *J Cancer*. 2021; 12(9): 2735–46).

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 was 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 [21, 22].

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.

In many laboratory studies, today are ongoing clinical trials with anti-CTLA-4 and immunological control points, ex. PD-1 / PDL1 can improve the prospects of patients with various malignancies [23]. 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, *Figure 3*, [24].

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. Additionally, this genetic information will likely play an increasing role in directing treatment.

COMPETING INTERESTS

The authors have no competing interests to declare.

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