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New Extended Investigations In Breast Cancer Diagnosis, Including Mirnas – Short Review

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Abstract
Background. Breast cancer impacts over one million patients worldwide annually, with prognosis influenced by clinical and biological factors such as age, tumor size, nodal involvement, and histological grade. Objective. The aim of this short literature review was to highlight the role of miRNA in breast cancer, showing that aberrant miRNA expressions in this type of cancer play a pivotal role in cancer prognosis. Methodology. This brief review includes the latest data published in the speciality literature which demonstrated that aberrant miRNA expression in breast cancer, associated with BRCA1 and BRCA2 gene mutations, present a poor prognosis after conventional oncological treatment. Results. The mutated BRCA1 and BRCA2 genes are among the most critical genetic markers associated with inherited breast cancer predisposition, along with mutations in the PTEN and P53 genes. Breast cancer susceptibility related to BRCA1 mutations can reach up to 87% in older women. Breast cancer treatments may include chemotherapy, hormonal therapy, surgery and/or radiotherapy, depending on the stage and molecular characteristics at diagnosis. Modern emerging therapies use and modify miRNA strands that naturally inhibit cell division. Conclusions. The authors conclude that understanding the genetic structure of breast cancer provides valuable scientific insights that can enhance the prediction of tumor aggressiveness in breast cancerand improve treatment outcomes.

Keywords: Inflammatory Breast Cancer, Triple-Negative Breast Cancers, P53 Gene, Isoform P53 Protein, Mirnas

Introduction
International statistics of breast cancer show that persons with BRCA1 and BRCA2 mutations have a significantly higher risk of developing this disease (45% to 65%) by the age of 70 yearsold [1].

It is recommended that individuals with these mutations have a genetic consult. Other risk factors of breast cancer include obesity, hormone therapy,with progestin or estrogen, abuse of alcohol and sedentarism [2].

The most severe forms of breast cancer occur when the tumour spreads in metastases to other parts of the body. The early diagnosis and new molecular treatments in breast cancer improved the outcomes of patients [3].

Despite these advancements, tumor recurrence and metastasis remain the leading causes of mortality for many breast cancer patients, posing significant challenges for reducing mortality rates, particularly in terminal cases. To improve

disease-free survival rates, investigating biomarkers associated with breast cancer cell metastasis is essential [4].

The first study analyzing gene expression patterns in breast cancer identified at least four major molecular classes: luminal-like, basal-like, normal-like, and HER2-positive. Factors such as histological type, tumor grade, size, lymph node involvement, estrogen receptor statusand HER2 receptor status significantly influence the prognosis and response to systemic therapies [5].

Methodology

Many studies have shown the roles of different microRNAs (miRNAs) in the development and progression of BC. Additionally, the wild-type p53 protein, reported to be reduced by more than 50% in various cancers has been identified as a potential genetic target for miRNAs of carcinogenic process [6,7].

This short review was based on published data that demonstrated abnormal miRNA expressions involved in the initiation and development of cancer, as well as negative mutations in the BRCA1 and BRCA2 genes in breast cancer. The criteria of analysis in this short review were reperezentedby data which demonstrated that the mutant BRCA1 and BRCA2 genes, besides another genes such as the mutant PTEN gene and P53 gene, present a hereditary predisposition to breast cancer, with a poor prognosis after treatment. In particular, mutations of the PTEN, ATM,BRCA and P53 genes are the sine quanon for the diagnosis of Li-Fraumeni syndrome. Also, the predisposition of P53 gene mutation may be associated with negative mutations in the BRCA1 and BRCA2 genes in breast cancer (Figure 1) [8].

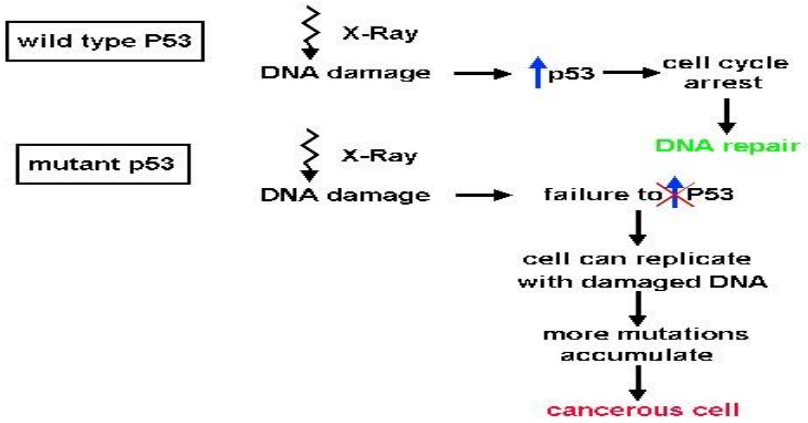

Figure 1: Effects of Isomorph P53 Protein In The Carcinogenesis Process, (Ozaki T, Nakagawara A. Role of p53 in Cell Death and Human Cancers. Cancers (Basel), 2011, APC Journal)

Results

Breast cancer susceptibility related to BRCA1 mutations can reach up to 87% in older women Basal-like breast cancers account for approximately 15% of breast cancer cases and are often classified as triple-negative breast cancers (TNBCs). These cancers are characterized by the absence of estrogen, progesterone and HER2 receptors and are frequently associated with younger patients and poor prognosis [9].

Angiogenesis is an essential factor in tumor growth and metastasis in various malignancies, including breast cancer. Increasing evidence demonstrates that angiogenesis is regulated by (miRNAs), which are small non-coding RNAs consisting of 19-25 nucleotides. Over the past 10 years, the roles of miRNAs have been extensively investigated across multiple types of human cancers. Evidence suggests that miRNAs regulate gene expression by targeting various molecules that influence the physiology and development of cancer cells. Depending on their functions in different tumor types, miRNAs are classified as either oncogenes or tumor suppressors. The same expression of miRNAs can contribute to chemoresistance, radioresistance and endocrine resistance in the treatment of breast cancer [10].

The P53 gene encodes a protein commonly referred to as the "guardian of the genome", which binds to DNA to regulate transcription, control the cell cycle and induce apoptosis, among other functions. According to epidemiological studies, the risk of developing cancer in patients with P53 gene polymorphisms is as high as 90%.The product of the P53 gene, the p53 protein, is a phosphoprotein consisting of 393 amino acids and contains four functional domains, one of which activates transcription factors (Figure 2) [11].

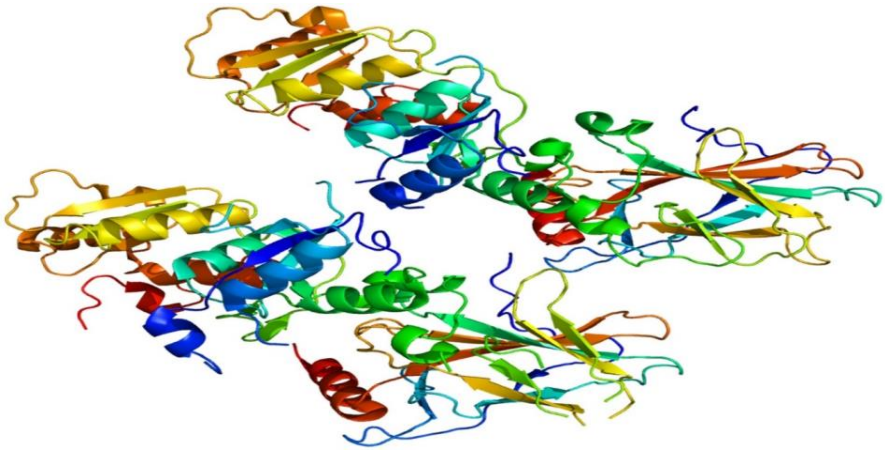

Figure 2: P53 Protein In Active Tetrameric Form, (Hamzehloie T, Mojarrad M, Hasanzadeh Nazarabadi M, et al. The Role Of Tumor Protein 53 Mutations In Common Human Cancers And Targeting The Murine Double Minute 2-P53 Interaction For Cancer Therapy. Iran J Med Sci. 2012, APC Journal).

Numerous studies have demonstrated that aberrant miRNA expression is involved in the initiation and development of cancer. Additionally, the native p53 protein, which has been reported to be decreased by more than 50% in various cancers, could be used as a target gene of miR-214 [12].

Discussion

Recent studies have shown that miR-124 contributes to the development and aggressive forms of malignancies, in tumor spread, epithelial-mesenchymal transition (EMT), metastasis and cellular resistance at chemotherapy. Particularly in breast cancer was found that the overexpression of miR-214 significantly enhanced cell invasion by down-regulating p53 expression [13].

For instance, breast cancer tissues have been shown to exhibit reduced expression of miR-124 compared with normal tissues. Thus, miRNAs are regarded as effective targets for further studies on the design of novel therapeutic strategies [14].

Also, the type of miR-124 overexpression has been shown to contribute to an increase in the number of cells present in the G0/G1 phase cellular cycle and inhibits STAT3 production. This miR-124 is a key modulator of cholinergic anti-inflammatory effects and can inhibit the expression of tumor necrosis factor beta, (TNF-β) (Figure 3) [15].

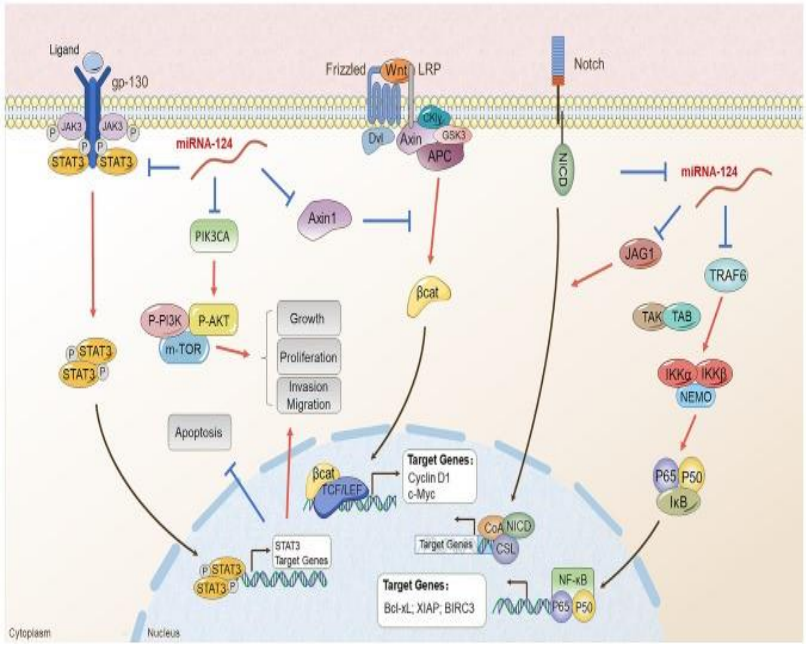

Figure 3: PI3K/Akt triggers A Signalling Cascade That Modulates Tumor Cell Proliferation. Servier Medical Art (Web site: https://smart.servier.com)

The PIK3CA gene is an oncogene part of the PI3K signalling pathway and is associated with cell proliferation and carcinogenesis in multiple tumor types. Also, the NF-κB has the role in the NF-κBsignalling system, in the initiation of angiogenic neovascularization, epithelial-mesenchymal transition (EMT), and development of cancer cells [16].

A target for cancer treatment must be the JAK/STAT signalling pathway which stimulates the molecular mutations in different cancer diseases [17].

Also, miRNA, miR-124, has been shown to have a beneficial role that can inhibit the migration and proliferation of certain cancer cell types and can be used in therapeutic strategies of breast cancer [18,19].

While the concept of reintroducing microRNA-34a into cancer cells may appear straightforward, researchers have faced numerous challenges in developing an effective therapy.It is well known that the membranes of cells in the human body have receptors that bind to folic acid and draw this vitamin into cells. Thus, the researchers attached a folate molecule vitamin with microRNA-34a to be inset in nucleus cells (Figure 4) [20].

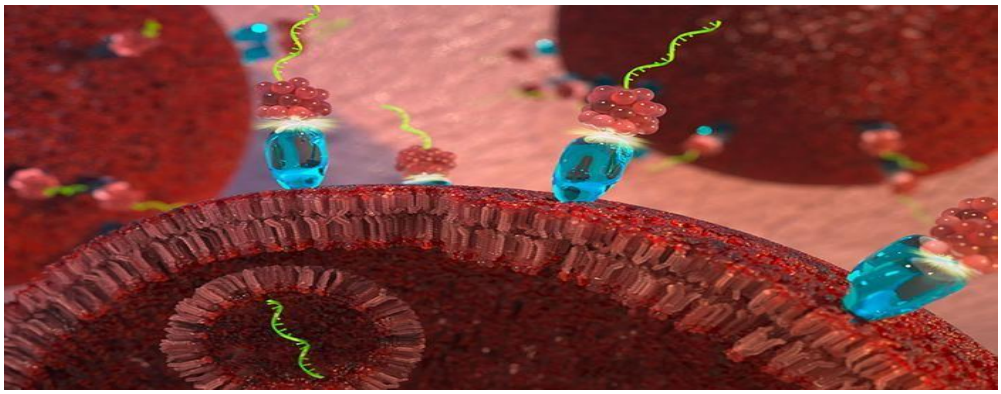

Figure 4: A Novel Therapy Targets Cancer Cells Using A Modified Strand Of Microrna That Naturally Inhibits Cell Division, (Li WJ, Wang Y, Liu X, et al.Developing Folate-Conjugated miR-34a Therapeutic for Prostate Cancer: Challenges and Promises. Int J Mol Sci, 2024; APC Journal).

Active immunotherapies also create a protective effect against neoplastic tissue by readjusting the immune system to a state of antitumor surveillance. In solid tumors like breast cancer, antigen (Ag), cells expression, differs from that of healthy cells. The differentiation of CD4+ and CD8+ T-cell responses is initiated by specialized antigen-presenting cells (APCs), such as dendritic cells (DCs). Ultimately, CD8+ T cells localize to tumor tissueand target and destroy cancer cells.However, due to its low antigenicity, immunotherapy is not recommended for ER+ breast cancer. Research findings indicate that various factors contribute to the reduced antigenicity of ER+ breast cancer, which is linked to decreased production of tumor neoantigens (neo-Ag). In recent years, significant research has also focused on anti-HER2 vaccines (Figure 5) [21].

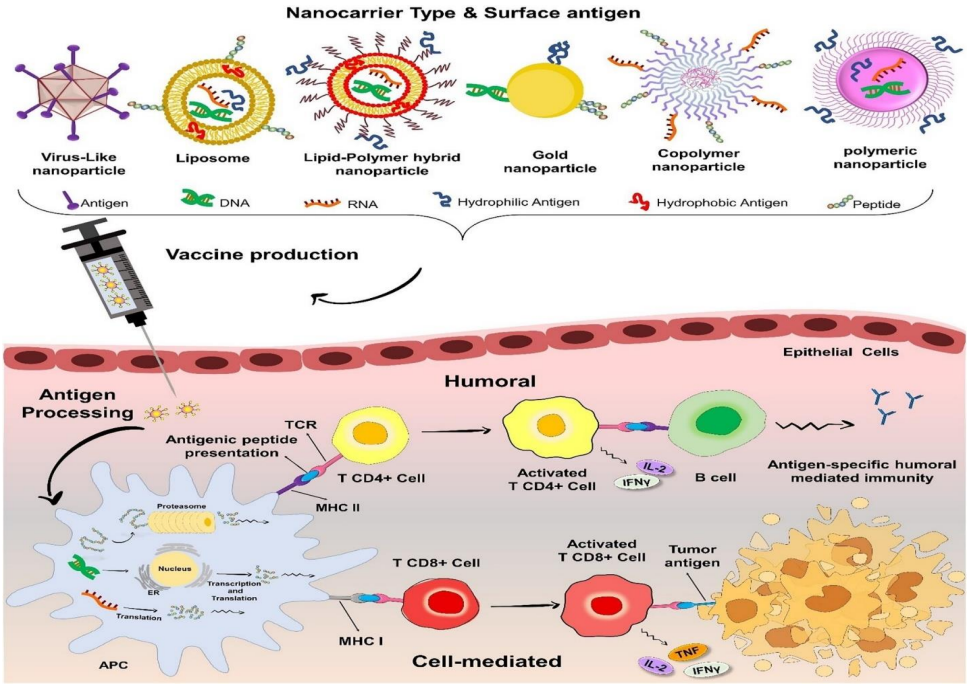

Figure 5: Anti-HER2 Vaccines Stimulate The Differentiation of CD4+ and CD8+ T cells Through Specialized Antigen-Presenting Cells (APCs), Such As Dendritic Cells (DCs), Ultimately Enabling CD8+ T Cells To Target Tumor Tissue (Personal Scheme).

The latest clinical studies of advanced breast cancer, after the conventional oncologic treatment, have shown that the presence of P53 gene mutations was associated with lower survival rates of the patients, but the activation of the non-mutant P53 gene, presented in another form of breast cancer, led to a complete inhibition of tumor growth by inhibiting the cytoplasmic oncogenic MDM2 protein (Figure 6) [22-24].

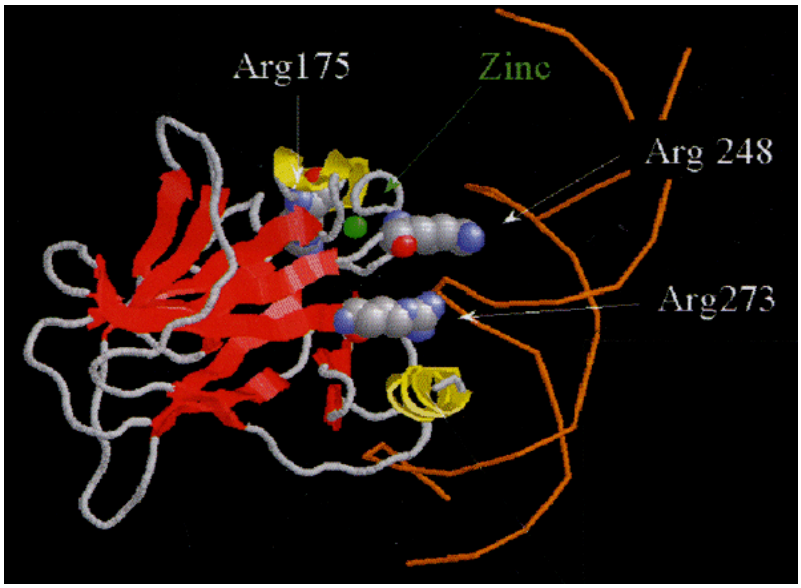

Figure 6: Three-Dimensional Representation Of The p53 Protein Structure In Its Isomorphic Form, Obtained Through X-ray Imaging. In Hereditary Cancer Clinics, Five Mutations Of The P53 Gene Have Been Identified, (Okorokov AL, Sherman MB, Plisson C, et al.The Structure Of p53 Tumour Suppressor Protein Reveals The Basis For Its Functional Plasticity, 2006, APC Journal).

In clinical trials, antibodies specific to the p53 isoform protein, combined with peptides derived from p53, have been used to evaluate immune responses in cancer patients with P53 gene mutations. Short-term in vitro stimulation with p53-transfected dendritic cells revealed that over 40% of breast cancer patients exhibited the reactivation of CD4+ and CD8+ T cells. Numerous laboratory studies and clinical trials are currently underway, investigating anti-CTLA-4 antibodies and immune checkpoints such as PD-1/PD-L1, which could improve the outlook for patients with various types of malignancies, includingBC (Figure7) [25,26].

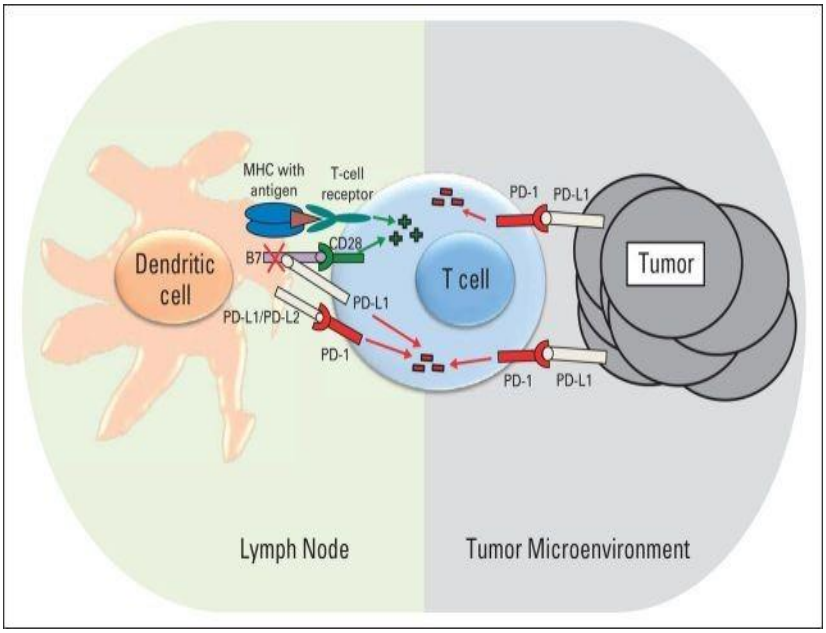

Figure 7: Interactio between T cells, anti-CTLA-4 and Immune Checkpoints Such As PD-1/PD-L1, (Wojtukiewicz MZ, Rek MM, Karpowicz K et al. Inhibitors of Immune Checkpoints-PD-1, PD-L1, CTLA-4-New Opportunities For Cancer Patients And A New Challenge For Internists And General Practitioners. Cancer Metastasis Rev. 2021, APC Journal).

CRISPR/Cas9, as an effective genomic engineering tool, now has a vital role in treating various diseases.The efficacy of cancer therapy is increased by the use of CRISPR/Cas9 gene editing technologies [27,28].

For example, the CRISPR technology can be used for miR-124 editing reduction.Also, latest studies demonstrated that

the hormonal therapy applied in breast cancer can be often combined with CDK4/6 inhibitor therapy, with very good response in disease evolution [29,30].

Clinically, the index of proliferative studies of different types of cancer–pKi67 protein index– has been shown to be higher in malignant tissues with poorly differentiated tumor cells compared to normal tissues. A past cutoff of 20%was established for classifying cancer tumors as highlyproliferative (Figure 8) [31].

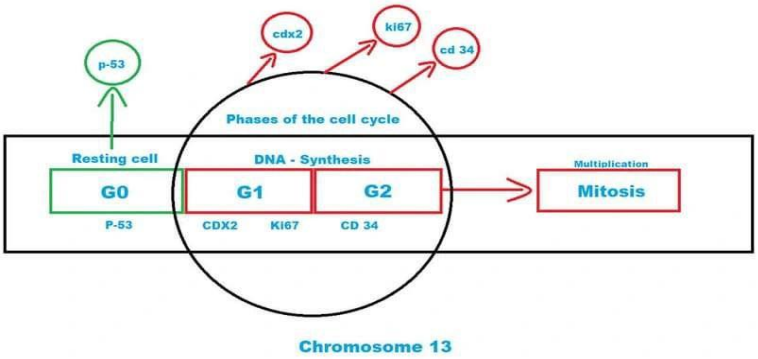

Figure 8: Ki67 As A Positive Or Negative Marker In A Tumor Biopsy Can Be An Oversimplification Of Its Role As An Indicator Of Tumor Aggressiveness (Personal Scheme).

The Ki67 protein has a half-life of approximately 1-1.5 hours. It is present during all active phases of the cell cycle (G1, S, G2 and M), but it is absent in resting cells (G0). In the later phases of mitosis (during anaphase and telophase), Ki67 levels decrease sharply. Studies on Ki67 have indicated that it undergoes proteasome-mediated degradation during the G1 phase and upon cell-cycle exit. Additionally, the depletion of Cadherin1 (Cdh1), an activator of the Anaphase Promoting Complex (APC/C), has been linked to altered Ki67 regulation [32].

Conclusions

The authors of this review conclude that genetic studies used to identify the genomics of malignant cells in breast cancer provide valuable scientific information and predictive data about tumor aggressiveness. In addition, the results of these studies could play an increasing role in guiding personalized oncology treatments in breast cancer with some types of RNA.

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