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A Comprehensive Review of Emerging Biomarkers ACNG4, CHRNA6, PKMYT1 And EPYC And Their Role In Breast Cancer Diagnosis And Treatment

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ABSTRACT

Breast cancer remains one of the most significant threats to women' health that calls for identification, development and improvement of diagnostic markers, prognostic indicators and therapeutic targets. Several molecular markers including HER2, ER and BRCA1/2 have contributed to the treatment of breast cancer but they are inadequate especially in the aggressive and therapy-resistant tumors like the triple negative breast cancer. The new biomarkers—ACNG4, CHRNA6, PKMYT1, and EPYC—provide better modalities than previous approaches by providing better understanding of tumor behaviour, diagnosis, and treatment. ACNG4 and CHRNA6 are potential biomarkers targets for early diagnosis and for enrolment of breast cancer aggressive subtypes while PKMYT1 is a promising biomarker owing to its implication in cell cycle regulation and EPYC for its implication in tumour microenvironment. However, some limitations such as patient variability and the absence of standardized detection mechanism become hurdles to the application of these approaches in clinical settings. To elaborate each biomarker's possibility and drawback, this review also evaluates the combination of those biomarkers with innovative technologies such as liquid biopsy and artificial intelligence to boost breast cancer treatment. Further studies and development of more elaborate approaches are needed in order to turn the biomarkers identified in this study into clinically stable and accurate measures that will help in the development of precision oncology and consequent individualized treatment protocols.

Keywords: *Breast cancer, Biomarkers, ACNG4, CHRNA6, PKMYT1, EPYC*

1. INTRODUCTION

Breast cancer has continually been ranked among the most common cancers that affect women across the world, with thousands of women's lives being put at risk every year [1]. Even with developments in therapeutic forms, an important factor is still the early diagnosis of a disease which will increase the number of people cured and reduce the volume of patients requiring invasive treatments. In recent years, biomarkers have become significant, since these aid in determining several factors, which affect the outcome of diagnosis, prognosis, as well as efficacy of treatment administered [2]. Established biomarkers in breast cancer include HER2 (human epidermal growth factor receptor 2), ER (estrogen receptor), PR (progesterone receptor) and BRCA1/2 (breast cancer susceptibility genes 1/2) which are commonly used clinically (figure 1)[6]. Some of these biomakers have been used not only in categorizing breast cancer subtypes but also in assigning therapeutic strategies as well as determining her prognosis [7].

However, these biomarkers have their own limitations when it comes to practice. The lack of available treatments for cancers that do not over-express HER2, ER or PR – also called triple-negative breast cancer (TNBC) is a significant void. TNBC constitutes 10-20% of breast cancer patients and has no specific treatment since there are no such receptors; the standard treatment is chemotherapy that comes with poor efficacy and high toxicity [8]. Furthermore, it has been found that although BRCA testing is helpful in estimating genetic risks, it does not work when it comes to addressing sporadic, non-hereditary breast cancers which are more common [9].

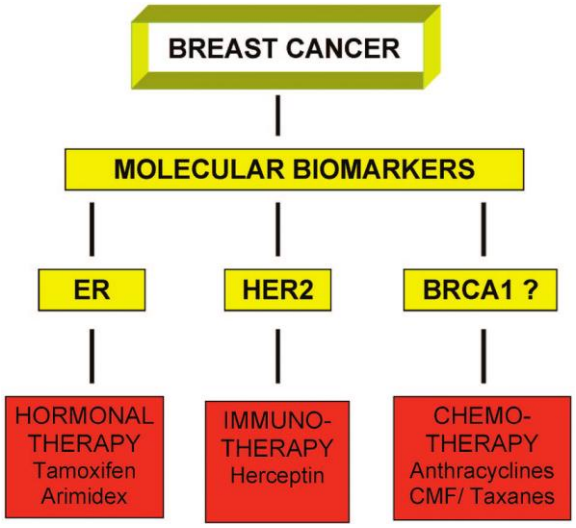

Figure 1: Schematic demonstrating current molecular biomarkers used in the clinical management of breast cancer [6]

In the attempt to identify novel biomarkers, more potential candidates have been examined, including ACNG4, CHRNA6, PKMYT1 and EPYC. These biomarkers hold promising capabilities of satisfying unmet clinical demands in breast cancer, opening up novel approaches to diagnosis and treatment which have not been feasible before [3]. For instance, ACNG4 has been considered that it is involved in breast cancer signaling and CHRNA6 has been evidently related to certain molecular pathways of cancer aggressiveness [4]. Whereas, PKMYT1 is associated with cell cycle regulation which could provide understanding of the growth patterns of the tumor. In the same way, the position of EPYC in cellular interactions makes it potential candidate for early diagnosis or monitoring [5].

This review is intended to present a description of the development of these new biomarkers and eleborate their diagnostic and therapeutic significance in breast cancer. The purpose of this study is to discuss and outline our understanding of ACNG4 and CHRNA6, and explore possible implications on breast cancer prognostic and treatment.

Emerging Biomarkers: ACNG4, CHRNA6, PKMYT1, and EPYC

Newer findings in molecular studies have disclosed several novel candidates for breast cancer biomarkers such as ACNG4, CHRNA6, PKMYT1, and EPYC. These new biomarkers are revealing new aspects of tumor processes, which opens a new perspective in the diagnosis, prognosis, and treatment [10]. They are intrinsically different in their molecular properties and activation in the context of cancer signaling, from other markers such as HER2 and BRCA1/2 genes, to meet the needs in breast cancer management [10].

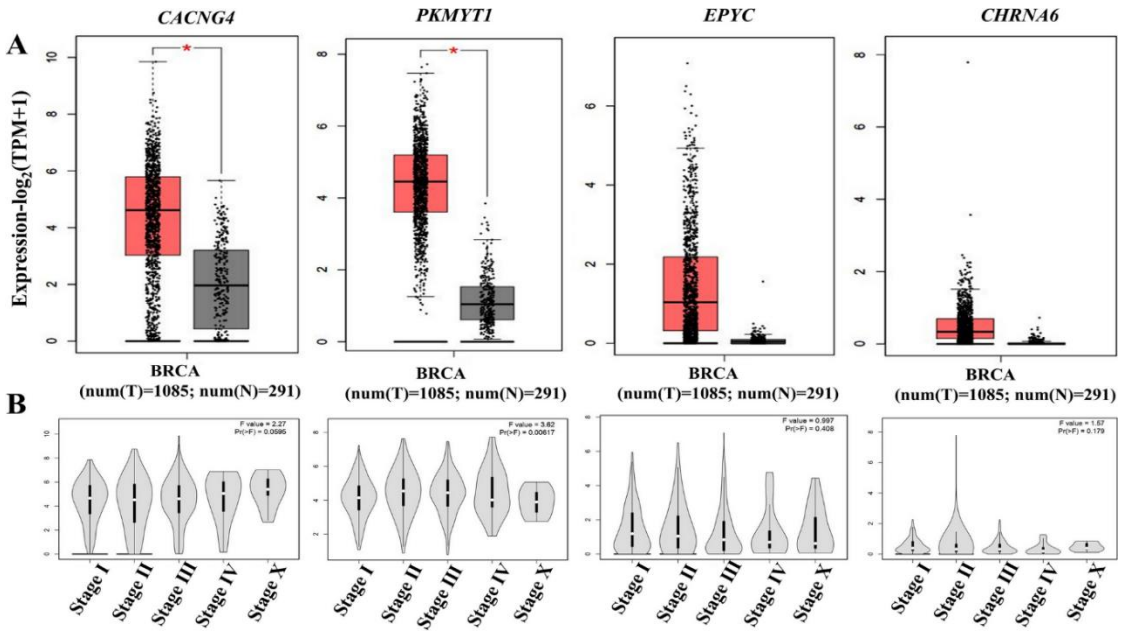

Figure 2: Expression analysis and stage correlation [1].

ACNG4 is one of the most promising biomarkers due to its molecular structure and activity in cellular conversions. This gene produces a protein that may be part of signaling pathways associated with cellular division and, consequently, tumor development [11]. It has specific domains in its molecular structure that participate in cell signaling and therefore may serve as a therapeutic target for causing interference in cancer cell communication. Immunohistochemistry (IHC) and quantitative polymerase chain reaction (qPCR) methods are normally used to detect ACNG4 with the possibility of estimating its grades in breast cancer tissues [12]. Because ACNG4 could be present at different stages of cancer development, it might be useful for early diagnosis and, potentially, prognosis; more work is needed to elucidate its diagnostic potential and clinical applications.

CHRNA6 has been identified to play an important role in different kinds of breast cancers, more specifically those that are characterized by high invasiveness of the tumor [13]. Being a member of the nicotinic acetylcholine receptor family, CHRNA6 is primarily associated with neural transmission and signaling but was recently implicated in the molecular pathways involved in cancer, including cell cycle control and apoptosis [14]. Its relationship with cellular processes associated with breast cancer reveals its potential as a molecular target for treatment, especially in the most malignant subtypes of breast cancers such as TNBC. CHRNA6 can be detected by gene expression profiles, which showed high expression in given subtypes of breast cancer and the results could be used to guide diagnosis and treatment.

PKMYT1 is or kinase and has been reported to be important for the regulation of cell cycle with particular emphasis on the G2/M checkpoint of the cell cycle. Specifically for breast cancer, it has been revealed that PKMYT1 promotes tumor growth and has a negative prognosis because it allows tumor cells to bypass cell cycle checkpoints and thus divide uncontrollably [15]. Clinical effects have highlighted PKMYT1 as a promising drug target especially in those conditions where conventional treatments prove to be unhelpful. PKMYT1 has been demonstrated to possess potential preclinical efficacy through its ability to halting the main cell division stages in cancer cells [16]. The techniques like Western blotting and RT-PCR is employed for identification of PKMYT1 in breast cancer cells and helps in its analysis in clinical and experimental models.

EPYC (epiphycan) is an ECM protein with roles in cellular communication within the surrounding environment of breast cancer. EIG12 is thought to participate in signaling pathways that are involved in tumor growth, metastasis, and resistance to treatment [17]. EPYC expression has been identified in various patients, which may indicate that this molecule is useful as a biomarker for population-based breast cancer research. This biomarker has been identified through immunoassays and in situ hybridization suggesting that would form part of a clinical diagnostic test which would be useful in determining the invasiveness of tumors and their likelihood to metastasize [18].

Altogether, the four genes, ACNG4, CHRNA6, PKMYT1, and EPYC could potentially supplement deficiencies of the current biomarker. Not only do they describe cancer cell functions including signaling, regulation and communication with the tumor microenvironment but also they identify potential targets for therapeutic intervention which may translate into a better prognosis for patients with breast cancer [19]. Expanding the identification strategies for these molecular targets as well as their relevance in clinical practice, these novel biomarkers can serve as the crucial part of individualized management of breast cancer patients, offering novel approaches in diagnosing, treating, and predicting outcomes for the disease [20].

Clinical Applications and Prognostic Implications

Novel biomarkers like ACNG4, CHRNA6, PKMYT1 and EPYC also have the potential to improve clinical outcomes in patients diagnosed with breast cancer due to developments in the diagnostic, therapeutic and prognostic abilities. The inclusion in clinical practice provides the concept of a 'multi-modal' therapy that may enhance patient survival and quality of life [21].

Diagnostic Applications: The value of these biomarkers for diagnostics is that they are specific in their expression and function in comparison to more familiar biomarkers such as HER2 and ER. For instance, since the expression of ACNG4 is associated with the first step towards the formation of cancer, it is a candidate for early diagnosis. This could help in early diagnosis of the disease so that management could be done at early stages of the disease process when treatment is still effective [22]. Moreover, CHRNA6 due to its selective expression in metastatic breast cancer cells is informative for IHC testing particularly for TNBC that does not have known actionable biomarkers [23]. The inclusion of these biomarker results in the diagnosis could give a better idea of cancer subtype and its potential aggressiveness on the onset of treatment.

Therapeutic Applications: It is therefore obvious that these biomarkers involved in cellular signaling pathways could be valuable targets for such therapies. This protein, for instance, is involved in cell cycle regulation and its dysregulation could hinder cancer cell division particularly those hard-to-treat cancer patients. Targeting PKMYT1 might enhance current treatments since it is an independent pathway that can be used to prevent tumor proliferation if conventional therapies do not work [24]. EPYC could alter the extracellular matrix and thus possibly limit the spread of the cancer, as well as potentiate the outcomes of the existing chemotherapy treatments [25]. Interventions aimed at altering EPYC might prevent metastasis in patients with high risk, especially in aggressive subtypes of breast cancer.

Prognostic Value: The emerging biomarkers of these proteins also provide vital prognostic information, mainly encompass the expression levels. For example, high PKMYT1 levels are associated with poor diagnostic indicators; therefore, the levels of this protein are used to determine the severity and potential for cancer relapse [26]. Patients with high levels of ACNG4 or CHRNA6 may also benefit from additional monitoring interventions to detect cancer early because they are linked to higher tumor proliferation and metastatic potential [27]. Using these biomarkers in creating prognostic models, clinicians are then able to sort patients according to risk in order to have more personalised, targeted managed care that may well elevate survival rates.

Personalized Medicine and Treatment Optimization: Implementing the biomarkers ACNG4, CHRNA6, PKMYT1, and EPYC into clinical practice could be the foundation of the future of breast cancer treatment. Therefore, efficient pattern recognition of biomarker profiles in each patient enables oncologists to prescribe therapies based on the patient's tumor characterization. This approach not only reduces the harm of side effects that are common in broad-rum treatments but also enhances the effectiveness of the treatments, especially for resistant or high risk cancer [28]. Such biomarkers could help steer patients toward specific management protocols that may prevent relapse and enhance the patients' overall quality of life.

These genes, ACNG4, CHRNA6, PKMYT1, and EPYC, have potential diagnostic, therapeutic, and prognostic values, complementing the existing approaches in breast cancer management. Because of their involvement in cellular signaling and tumor growth, they hold the promise of enhancing cure germination and enhancing individual results, signifying the advancement towards superior therapeutic option and Patient-Centric Cancer Treatment [29].

Challenges and Limitations

ACNG4: Although, ACNG4 has potential as biomarker for diagnosis and prognosis of breast cancer, several issues hinder its usage in clinic today. The first limitation is that there is no uniformity in the detection methods. In contrast with official markers like HER2, ER, where there are common protocols for testing, till the present moment there are no common detection methods for ACNG4, which contributes to the differences in results obtained in various laboratories or trials [10]. More importantly, the function of ACNG4 in breast cancer has not been clearly elucidated at the biological level. Discovered as a potential tumor-associated gene possibly involved in signaling pathways of cancer genesis, more investigation must be done in order to determine its precise effect within the breast cancer molecular subtypes, thus the current role of ACNG4 as a treatment marker remains relatively limited [30]. To overcome these issues, larger sample size studies should be conducted to establish the mode of action of ACNG4, optimize the method of detection, and determine its prognostic performance in various population cohorts [31].

CHRNA6: CHRNA6 has been recently associating with breast cancer, but it is yet to realize practical clinical use due to several problems. An important problem is that COX is engaged in complex regulation of signaling in cells. CHRNA6 is encoded as a member of the nicotinic acetylcholine receptor family of proteins, of which for the most part has been described in neurological disorders rather than in cancer. It is related to cancer related pathways, their roles are still unclear, and therefore it is hard to estimate its activity and impact on the development of breast cancer. This is a major challenge in the formulation of therapies or interventions that are tailored to CHRNA6, as the protein's function and relation to other cellular processes are not well understood [32]. Furthermore, there are no standard methods for examining CHRNA6 including

detection techniques that are still proving as research tools in development. Gene expression assays, used currently, need to be worked out more well to achieve a high level of sensitivity and specificity. [33].

PKMYT1: PKMYT1 is a promising biomarker in breast cancer especially because of its role in cell cycle regulation. Nevertheless, at present, several limitations are an issue, and they prevent the usage of this classifier in the clinical practice. One major limitation is the specificity of PKMYT1 as the biomarker. Despite the enhancement of cell cycle progression in breast cancer, this mechanism involving PKMYT1 is probably involved not only in breast cancer but also in other types of cancer. This lack of specificity dilutes its potential as a separate marker specific for breast cancer only and if this PKMYT1 is high then it could mean the presence of other forms of cancer [34]. Another drawback is associated with a heterogeneous distribution of PKMYT1 levels in individual classes of breast cancer. Though distinguishing the malignant from the benign colorectal neoplasm its expression is more evident in a more aggressive form and higher stage of cancer, which reduces its sensitivity in the early diagnosis of cancer. Perhaps, it is more suitable for assessing the disease progression or, indeed, the risk of the disease recurrence rather than for screening. This limitation hinders the versatility of PKMYT1 in other diseases thus the very application of PKMYT1 in breast cancer may be confined more in diagnosing breast cancer in special circumstances and not for general screening purposes [35].

EPYC: EPYC (epiphycan) has received significant interest as a biomarker in breast carcinoma because it is involved in the components of ECM as well as cell signaling network. Nevertheless, difficulties in the clinical use are still observed. A major drawback of EPYC is its multifunctionality in the context of the tumor microenvironment. EPYC is expressed in cell adhesion an communication within the ECM, while its exact roles in tumor growth, metastasis and progression are still unknown. These facts let alone explaining how to use EPYC for the adjuvant therapy or molecular marker, because it differs in interaction with the ECM depending on specific molecular characteristics of the tumor [36]. Furthermore, the detection methods of EPYC, namely immunoassays and in situ hybridization are not fully optimal for routine clinical use. These methods require harmonisation and calibration to reduce bias that might lead to low credibility of EPYC in clinical practice. Also, the expenses concerning these asserts would limit their application on large scale screening, especially in regions with scarce resource endowment. Solving these technical issues is critical to furthering the purpose of EPYC in breast cancer therapy [37].

2. CONCLUSION

The identification of these new biomarkers – ACNG4, CHRNA6, PKMYT1, and EPYC, is crucial to improving the understanding of Breast cancer diagnosis, prognosis and management. Each of these biomarkers fills the gap created by the more established biomarkers such as HER2, ER, PR, and BRCA1/2 to open up more avenues for understanding of tumor related characteristics as well as disease management. Thus, such genes as ACNG4 and CHRNA6, may be used for early diagnosis and could be more effective in triple-negative breast cancer – a particularly severe type of the disease which treatment strategies are rather limited. Hence, PKMYT1 as a cell cycle regulator is a promising prognostic biomarker and a therapeutic target; EPYC that is implicated in the functions of the tumor microenvironment can help explain metastasis and treatment resistance.

However, there are still some limitations in putting these biomarkers into the clinical applications. Factors like variation in expression in patients at different age, gender and ethnicity, the absence of definitive methods of the detection of these biomarkers and limited understanding of the complete biological function of these molecules keep these biomarkers from translating into clinically useful biomarkers.

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