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Breast Cancer microRNAs as Clinical Biomarkers

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Abstract

Breast cancer is the commonest cancer among women worldwide. Despite the rising incidence of the disease, significant improvement in breast cancer patient outcomes has been observed in recent years. These improved clinical and survival outcomes coincide with our enhanced appreciation for the processes of cancer development as well as the advances in therapeutic strategy for breast cancer patient management. In recent times, the translational research paradigm has evolved to understand that microRNA (small, non-coding molecules, 19-25 nucleotides in length) are key modulators in oncogenesis. Monitoring miRNA expression patterns is perceived to be informative in predicting response to conventional breast cancer therapeutics and providing prognostication. This Mini-Review will provide a concise summary of current efforts to exploit aberrant miRNA profiles to identify novel therapeutic targets and the focus on correlating miRNA expression levels with response to current treatment strategies.

Keywords: Breast cancer; microRNA; Non-coding RNA; Precision oncology; Personalized medicine

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Introduction

Breast cancer is the commonest cancer amongst women, with 2.3 million new diagnoses made in 2020 [1]. The incidence of breast cancer is increasing annually, but a greater understanding of the underlying biochemical processes of the disease has contributed to a decrease in mortality rates by 2%-3% per year in developed countries. Improved disease management and recent advances in personalized treatment regimens for breast cancer patients has led to a significant improvement in the anticipated 5-year survival rates from 40% to 87% [2]. Such advances have been facilitated through the identification of novel biomarkers, which are useful to estimate patient prognostication, predict outcome, and offer new therapeutic targets to dampen cancer progression.

A biomarker, a portmanteau of 'biological marker', is a characteristic that is objectively measured as an indicator of normal biological processes, pathological processes, pharmacological responses to a therapeutic intervention [3]. Traditionally, clinicopathological characteristics including age at diagnosis, tumour grade and disease burden were used to estimate prognoses and anticipate patient outcomes. Our increased understanding of the biomolecular processes driving oncogenesis have led to the discovery of biomarkers such as Estrogen Receptor (ER), Progesterone Receptor (PgR), HER2 and Ki-67 proliferation indices, all of which are crucial in the differentiation of the disease into four distinct intrinsic biological subtypes; these are Luminal A (LABC), Luminal B (LBBC), Human Epidermal growth factor Receptor-2-enriched (HER2-positive) and Triple-Negative Breast Cancer (TNBC) [2]. In recent times, translation research efforts have been focused on the discovery of novel biomarkers which may further enhance clinical outcomes for those who succumb to breast cancer diagnoses. This review focuses on the role of micro-RNA (miRNA) as emerging clinical biomarkers within the context of breast cancer surgery and treatment.

microRNA

microRNAs (miRNAs) are short, non-coding RNA (ncRNA) molecules 19-25 nucleotides in length. miRNAs are endogenous biomolecules which play a major role in the regulation of gene expression [2]. Within the nucleus, miRNA genes are transcribed by RNA polymerase II/III to form a primary miRNA (pri-miRNA) transcript, which subsequently undergoes a series of modifications to form mature miRNA. The mature miRNA strand forms part of the miRNA-associated RNA-Induced Silencing Complex (miRISC), which is responsible for guiding the RISC to target messenger RNA (mRNA) sequences by complementary base pairing. This guide functions of miRNA triggers silencing or degradation of mRNA, ultimately impacting on cellular activity [2,4].

Aberrant miRNA expression profiles are known to play a role in oncogenesis; the nomenclature 'oncomir' relates to increased expression during oncogenesis, while tumour suppressor miRNA have reduced expression in cancer [5]. Identifying such biomarkers may prove useful to aid diagnostics and prognostication, while the potential for utilising miRNA as therapeutic targets to enhance current treatment strategies [6]. As summarised in the recent

review by Davey et al. [2], there is emerging data supporting the reintroduction of specific tumour suppressor miRNAs to slow down or even halt oncogenesis [7]. Furthermore, the recent work of Di Cosimo et al. supports miRNA as useful biomarkers in identifying sensitivity to NAC in the setting of locally advanced HER2-positive disease [8].

MiRNAs as Breast Cancer Biomarkers

Despite the novel taxonomy of breast cancer into its four molecular subtypes, there remains heterogeneity in tumour activity within subtypes, variation in observed clinical outcomes, and varying responses to current multimodal therapeutic strategies [2]. Such issues present significant challenges to the current breast cancer treatment paradigm, thus highlighting the requirement for novel targeted therapies to specifically treat varying forms of the disease. The personalization of treatment in this manner is known as precision oncology.

In recent times, there has been a huge effort focusing on the identification of biomarkers capable of predicting patient response to neoadjuvant chemotherapy (NAC). There has been a trend in recent times to measure miRNA expression profiles and assess their role as predictive biomarkers of response to NAC [9]. Similarly, miRNA measurement has been correlated to chemoresistance in previous clinical studies. As summarized by Davey et al. miR-21 has a well categorized association with oncogenesis [2]. There are numerous studies which have correlated aberrant miR-21 expression profiles to patient response to NAC **(Table 1)**.

In the clinical trials Ireland All-Ireland Cooperative Oncology Research Group (CTRIAL-IE ICORG 10/11) prospective, multi-centre translational trial, the prognostic ability of circulating systemic miRNAs, including miR-21, was assessed [9]. This study concluded that miRNAs associated with breast cancer circulate the body and are present in detectable quantities in the blood of breast cancer patients. miR-21 and miR-195 were significantly down regulated in responders when compared with those who did not respond to NAC [9]. Interestingly, Kolacinska et al. outline the association of other miRNA molecules with TNBC patient response to preoperative chemotherapy [14]. In the same study, miR-200b-3p and miR-190a were overexpressed in those who demonstrated a favourable response from treatment alongside the under-expression of miR-512-5p [14]. Similar to commercially available multigene expression assays, miRNA panels (or miRNA signatures) are useful in predicting therapeutic targets and outcomes in operable breast cancer [15,16]. Elango et al. illustrate the clinical utility of a novel 40-miRNA expression panel predictive of lymph-node metastasis [17], while also highlighting the value of miR-205 and miR-214-3p in predicting poorer Overall Survival (OS). Other studies outlining the predictive value of miRNA signatures are outlined in **Table 2**.

Table 1: Studies correlating miR-21 expression profiles to patient response to NAC.

Author	Year	Country	LOE	Number of participants	Neoadjuvant treatment	miR-21 expression profile
De Mattos-Arruda, et al. [10]	2015	Spain	Retrospective (III)	52	Anthracycline, DTX & Trastuzumab	Overexpression of miR-21 in tumour tissue correlated to treatment response in HER2+ breast cancers.
Liu, et al. [11]	2019	China	Retrospective (III)	83	DTX, Paraplatin &Trastuzumab	Decreased miR-21 levels in serum correlated to response to NAC.
Liu, et al. [12]	2017	China	Retrospective (III)	118	EC & DTX	Up regulation of miR-21 in serum correlated to response to NAC.
Chekhun, et al. [13]	2020	Ukraine	Retrospective (III)	182	5-FU, DXR & Cyclophosphamide or DXR & Cyclophosphamide	Serum miR-21 levels used as a predictive marker for response to NAC in Luminal A breast cancers.

Abbreviations: LOE: Level of evidence; DTX: Docetaxel; EC: Epirubicin and cyclophosphamide; 5-FU: 5-Fluorouracil; DXR: Doxorubicin; HER2: Human epidermal growth factor receptor-2; NAC: Neoadjuvant chemotherapy

Table 3: Studies correlating multi-miRNA signatures to patient response to NAC.

Author	Year	Country	Tissue	Number of participants	miRNA expression signatures predicting OS
Cheng, et al. [18]	2018	China	Tumour & TAN	1207	Three miRNA expression signatures; miR-133a-2, miR-204 and miR-301b
Shi, et al. [19]	2018	China	Tumour	1098	Three multi-miRNA signatures; miR-16-2, miR-31 and miR-484
Lai, et al. [20]	2019	China	Tumour & TAN	1044	Six miRNA signatures; miR-147b, miR-549a, miR-4501, miR-4675, miR-6715a and miR-7974

Abbreviations: OS: Overall survival; TAN: Tumour-associated normal

Discussion

Limitations, challenges and future perspectives

Inconsistencies in sample preparation, storage, treatment and amplification protocols significantly limit the accuracy and reproducibility of results obtained through miRNA profiling. Despite these shortcomings, consensus has yet to be reached in relation to the most appropriate medium for miRNA testing. Although whole blood is commonly used, there are data suggesting circulatory miRNA levels may be impacted by circulating cancer cells [21]. Furthermore, the reliability of plasma and serum for miRNA measurement is mooted. Thus, it seems imperative that standardisation protocols for the quantification of miRNAs are necessary to overcome the challenge of heterogeneity and variability of results obtained.

Despite significant efforts, miRNA levels are yet to be normalised, and no universally accepted reference miRNA targets are tested as routine. The paucity of such reference miRNA renders the comparability of results more challenging to the scientist, bringing into question the validity of reported results. However, even if accepted standardized of reference miRNAs became established, the challenge of correlating standardization across all lifestyle and environmental factors (e.g.: patient age, gender, smoking habits etc.) is likely to prove challenging [2].

Conclusion

In conclusion, the fundamental involvement of miRNAs in the regulation of cellular activity provides great potential to harvest their activity to enhance therapeutic strategies in prospective breast cancer treatment. The identification of specific biomarkers, such as oncomirs or tumour suppressor miRNAs, remains key in the development of personalized anti-cancer therapies. Thus, the inherent value of preclinical studies evaluating miRNA expression profiles may indirectly lead to enhanced clinic-oncological outcomes. In the future, therapeutic strategy may include the manipulation of miRNA expression patterns as an attempt to enhance tumour activity-this provides rationale for the current emphasis on measuring and evaluating the clinical utility of miRNA as informative biomarkers for breast cancer patient management.

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