Hotspot of Precision Medicine for Breast Cancer: A Mini Review

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Abstract

Nowadays, most efforts focus on detecting the value of prognostic and predictive tools in the subject of breast cancer kept moving. According to the review of breast cancer research recently precision medicine is still a hot topic with new achievements. In this review, we discuss recent advances on the precision medicine for breast cancer such as genome sequencing, liquid biopsy, single cell sequencing exosomes.

Since president Obama had announced a science’s project initiative that aims to usher a new era of precision medicine. People has been widely accepted the concept of precision medicine [1]. Precision medicine involves the use of biomarkers to create individualized treatments and accurate diagnosis [2]. Biomarkers have become increasingly important in cancer treatment for prognosis and for guiding treatment decisions [3]. Precision medicine in breast cancer is based on results of tissue sampling and assay of the primary breast tumor and metastatic sites, for example assaying the estrogen receptor to select the most suitable treatment for every patient who may be benefit from endocrine therapy [4] According to the review of breast cancer research recently, precision medicine is still a hot topic, with new achievements in gene sequencing, liquid biopsy, exosome and so on. Meanwhile, the development of precision medicine is not always smooth. There is a long way to go before accurate diagnosis and treatment are achieved. In this review, we discuss recent advances on the precision medicine for breast cancer and highlight their relevance to understand the metastatic process and to guide therapeutic treatment for every patient who may be benefit from endocrine therapy [4] According to the review of breast cancer research recently, precision medicine is still a hot topic, with new achievements in gene sequencing, liquid biopsy, exosome and so on. Meanwhile, the development of precision medicine is not always smooth. There is a long way to go before accurate diagnosis and treatment are achieved. In this review, we discuss recent advances on the precision medicine for breast cancer and highlight their relevance to understand the metastatic process and to guide therapeutic

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Medical Exploration | 1: 1 | DOI: https://doi.org/10.32772/journal.v1i01.1 | www.medicalexploration.org/
interventions.

**Genome sequencing**

The decision to recommend adjuvant therapy for breast cancer used to depend on TNM staging system and then the immunohistochemical phenotype, currently, most of the treatment options are made under the diagnosis from molecular genetic pathology. Genome sequencing is a part of molecular genetic pathology. It has been used to find a lot of gene mutation sites, which makes the study on genes of breast cancer progress [5].

The hotspot of genome sequencing is the next generation sequencing (NGS). Compared with the method in the past, the next generation sequencing technique has the advantages of high accuracy high speed and high throughput [5]. A research confirmed that the next generation sequencing is much more sensitive [6]. NGS is mainly used to RNA transcription genome DNA sequence analysis and epigenetic sequencing in breast cancer research. Specific miRNA abnormalities were connected with specific types of breast cancer. For example, miRNA was associated with invasive carcinoma [7]. Triple negative breast cancer is lacked of unique miRNA expression, while most of miRNAs are connected with breast cancer metastasis.

Multiple gene detection is a part of genome sequencing and play an important role in hereditary risk assessment for breast cancer [8]. NCCN clinical practice guidelines have recommended multiple gene detection for breast cancer [9]. Both 21-gene and 70-gene detection are used to monitor the invasion or growth of the tumor, hormone-related protein which are helpful to analysis the risk of tumor recurrence and the effects of hormone therapy [9]. Cardoso et al. research recommended that the multiple gene detection has been revealed to improve prediction of clinical outcome in patients diagnosed with early-stage breast cancer, especially the 70-gene signature test [10]. 6693 women diagnosed with early-stage breast cancer were enrolled in this randomized, phase 3 study. The research determined their genomic risk with the 70-gene signature and the women’ clinical risk with a modified version of Adjuvant. The patients confirmed to be high clinical risk and genomic risk only need to receive chemotherapy. While the patients detected with discordant risk results were determined to receiver chemotherapy by the genomic risk or the clinical risk. The initial goal was to assess whether, the lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis would be higher than 92% among the women with a low-risk gene-expression profile who did not receive chemotherapy and high-risk clinical features. Finally, there are 1550 patient were deemed to be at low genomic risk and high clinical risk totally. After 5 years follow up, 94.7% patients of the group survival without distant metastasis compare with those not receiving chemotherapy. These patients’ survival rate was absolutely different to those
who received chemotherapy, with the rate being 15 percentage points lower without chemotherapy. The result was similar to the subgroup of patients who had ER(+)HER-2(-) and either node negative or positive disease. Among women diagnosed with early-stage breast cancer who were at both high clinical risk and low genomic risk for replace, the receipt of chemotherapy led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points higher than the rate without chemotherapy. Given these findings, the multiple genome detection and NGS are useful for doctors to select patients who are at really high clinical risk. Until now, the genome sequencing can only be applied to clinical trial without specification.

**Liquid biopsy**

A liquid biopsy, also named as fluid phase biopsy or fluid biopsy, is the sampling and analysis of primarily blood and non-solid biological tissue [11]. This technology which be liked to traditional biopsy is mainly used as a monitoring and diagnostic tool for diseases such as cancer, with the benefit of being largely non-invasive. And the technique has proved beneficial for patients after medical treatment to validate the efficiency of a cancer treatment drug and monitor recurrence. Liquid biopsy is consisted of circulation tumor cells (CTC), HER-2 extracellulra domain (ECD) and circulating tumor DNA (ctDNA). The CTCs technology has advanced from simple cell counting into era of molecular subtyping [12-14]. ECD and ctDNA could provide added value for breast cancer management and have potential clinical utility to detect biomarker from HER-2targeted therapies [15, 16].A multicenter and prospective study including response to HER-2 targeted agents FS and OS was to evaluate the potential utility of circulating tumor cell measurements in predicting outcomes to anticancer therapies [13].Three hundred patients with metastasis breast cancer planned to complete two imaging studies and three CTC blood draws. Finally, enumeration of CTCs in the MBC patients is an independent factor associated with PFS and OS, and provides substantial prognostic information. Moreover, the research demonstrated the prognostic worth in the various subtypes, such as HER-2(+) disease irrespective of therapy.

Another study was initiated to distinguish the difference between tumor tissue and CTCs in HER2 status, as well as the predictive worth of CTC HER2 status for predicting the prognostic of anti-HER2 therapy in histologically HER-2(+) metastatic breast cancer patients [14]. The result of the study showed that HER-2 status on CTCs was different from both of tumor tissues and predicted a different prognostic of the patients' anti-HER2 therapy. This difference may be related to CTC HER2 testing and the time interval between tissue, while indicating real-time HER2 analysis for histologically HER-2(+) MBC patients is necessary.

There are many clinical trials showed the ctDNA detection is a potential biomarker for prognosis of breast cancer, the diagnosis and management [17-20]. ctDNA detection can
provide a more accurate diagnosis for patients to guide clinical treatment in precision medicine era.

**Single cell sequencing**

Single cell sequencing provides a better interpretation of the function of a different cell in the context of its microenvironment and a higher identification of cellular differences [21]. Single cell sequencing is consisted of single-cell separation, single-cell immunohistochemical technique, single cell sorting and cloning, single cell genome sequencing and so on.

scDNA-seq involves constructing sequencing libraries, performing whole-genome-amplification, isolating a single cell and then sequencing the DNA through a next-generation sequencer. When the first time of sequencing novel species, it can be used in metagenomics studies. What’s more, it can be combined with high throughput cell sorting of cancer and microorganisms. The picture below showed how the single call genome sequencing work.

The emerging application of scDNA-seq is cancer sequencing. It is particularly useful for testing the depth of compound and complexity mutations show in amplified therapeutic targets like receptor tyrosine kinase genes.

scRNA-seq provides the presentation profile of individual cells. RNA still needs to be converted to cDNA for sequencing in the current scRNA-seq protocols. Principally, the following steps are contained in the current scRNA-seq methods: library generation and sequencing, isolation of single cell and RNA, amplification, reverse transcription. The picture below showed how the single call RNA sequencing work. scRNA-seq could be applied to different kind of cancer cells from normal blood cells and then obtain the presentation profiles of cancer cells at the same time.

Similarly, single cell RNA-seq can also be useful for analyzing rare cell types in early human adult stem cells and embryo, both of adult stem cells and embryo exist transiently. Additional, both of them are difficult to be characterized with current technologies.

In 2011, Navin investigated tumor population evolution and structure in two human breast cancer cases, using single-nucleus sequencing [22]. 100 single cells were analyzed from a polygenomic tumor.

The research revealed three distinct clonal subpopulations which many represent sequential clonal expansions. In additional, 100 single cells came from a monogenomic primary tumor was analyzed. And its liver metastasis showed that a single clonal expansion came in to being the primary carcinoma and seeded the metastasis. In primary tumor, they also confirmed an unexpectedly load subpopulation of genetically diverse dissimilar ‘pseudodiploid’ cells which do not transfer to the metastatic site. Their data recommend that carcinoma grow by punctuated clonal expansions with few persistent intermediates in the contrast for gradual models of tumor progression.

Another author achieved 91% mean coverage breadth by developing exome single cell and a whole-genome sequencing approach [23]. Their data reveal that remained highly stable as the
tumor masses clonally expanded and aneuploid rearrangements occurred early in tumor evolution. In contrast, point mutations generating extensive clonal multifariousness evolved gradually. A lot of the diverse mutations, using targeted single molecule sequencing, were shown to happen at low frequencies in the carcinoma mass. Additional, they found that ER(+) tumor cells had not an increased mutation rate, while the triple-negative tumor cells did [23]. These findings have important implications for evolution of chemoresistance, therapeutic treatment and the diagnosis in breast cancer.

Single-cell sequencing technique have intensively developed in the last few years. The technique presented many advantages for low quantities of available biological materials and solving the question of biological heterogeneity [24]. The understanding of a series of biological phenomena have been changed by the application of single-cell technique, including carcinogenesis embryo development and gene transcription [24].

**Exosomes**

Perhaps all eukaryotic fluids are present cell-derived vesicles where the exosomes from, including cultured medium of cell cultures, urine and blood [25, 26]. They are stable and biologically active, meanwhile they could be captured and detected in real time. The bioactive molecules, which exosomes carry, are involved in the communication among tumor cells, between atromal cells and tumor cells in the tumor microenvironment, affecting tumorigenesis, tumor growth, invasion and metastasis.

Exosomes are often described as 30–120 nm [27]. It is consisted of a complicated composition of molecules, including mRNA,
lipids, proteins and microRNA. The most common exosomal proteins are phospholipases, membrane transporters and fusion proteins, MVB synthesis proteins, tetraspanins, heat shock proteins and lipid-related proteins [28]. The participation of exosomes in breast cancer resistance, progression and development is becoming increasingly clear from preclinical study and clinical studies, with mounting more and more interest in the potential resource of these vesicles for biomarkers, and in the development of future novel breast cancer therapies [29, 30] (Figure 1). Carry, are involved in the communication among tumor cells, between atromal cells and tumor cells in the tumor microenvironment, affecting tumorigenesis, tumor growth, invasion and metastasis.

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Exosomes (Figure 2) are increasingly confirmed as prognosticators and biomarkers of disease besides their role as vehicles of intercellular communication [31]. Exosomes are used as a cancer biomarker to predictor progression of cancer [32]. Exosomes are derived from sera and cells of patients with breast cancer. Exosomes instigate nontumorigenic epithelial cells in order to form tumors in a Dicer-dependent manner [33].

![Figure 2](image_url) | The known biological function of exosomes
research found that exosomes transmit proteins and nucleic acid between cancer cells and stroma cells as mediate communication [34]. After occurrence of cancers, the quantity and the contents of exosomes will change. Exosomes lead to drug resistance through the transfer of anti-cancer drugs outside tumor cells. With lower toxicity and immunogenicity, exosomes are significantly effective tools to transmit anti-cancer drugs [34].

Exosomes derived from pancreatic cancer could elicit premetastatic niche formation through a couple step process what be helpful to promote liver metastasis [35]. Le et al found that larger vesicles and exosomes can send message (miR-200s) from highly metastatic cells to poorly metastatic cells. This step plays an important role of increase the metastatic potential of the poorly metastatic cells [36]. After exposure to stromal exosomes, a subpopulation of breast cancer cells can initiate tumor formation and are resistant to therapy [37]. Shimoda and colleagues recommend that tissue inhibitors of metalloproteininase fight against tumor-promoting exosomes release by the stroma [38].

Although exosomes remain much mystery to solve. These studies take a step for us to learn more about extracellular vesicles. The way about exosomes use-and carry-the necessary machinery to render mature miRNAs, that exosomes derived from cancer cells are significantly different between those derived from cancer cells and noncancer cells, and that extracellular vesicles are able to mediate the transfer of molecules that influence metastatic potential [39].

In conclusion, the goal of precision medicine is to give the most effective treatment for each person’s breast cancer. We need to know everything about precision medicine. Precision medicine will make a difference for patients in the future. And it will put forth to fight against cancer for millions of people all over the world. Long as the way is we will keep on searching above and below. Patients have to understand how genes work on treatment and cancer. Pharmaceutical or insurance companies need to acknowledge the importance of these genetic markers [40]. By the way, IMPATC (integrated mutation profiling of actionable cancer targets) tumor profiling assay has been approval which means the future is coming on.

Acknowledgements none.


Funding none.

Competing interests none.

Ethics approval none.

Provenance and peer review Not commissioned; externally peer reviewed.

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