

The Application of Metabolomics in the Development of Novel Diagnostic and Therapeutic Tools for Breast Cancer

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Abstract

Breast cancer (BC) is widely studied due to its importance in the world public health. Currently, there are multiple standardized methods for its diagnosis including physical and molecular ones. The strategies for BC treatment are diverse; despite the availability of different therapeutic options, BC still remains one of the leading causes of cancer death in women. There is a need for novel diagnostic and therapeutic tools, and metabolomics approach could help us to develop them and to improve the already existing ones, which leads us to the possibility of a personalized treatment with reduced adverse effects and a better clinical outcome. Herein, we describe the targets that are currently being used in the diagnosis and treatment of BC and review the development of new ones based on metabolic alterations on BC. We conclude that a recent metabolomics approach can be a novel tool to improve the diagnosis of BC as well as constitute the basis for identification of new therapeutic targets.

Keywords: Breast cancer; Biomarkers; Catabolism; Pharmacometabolomics

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide [1]. Due to the current screening programs that include mammogram, ultrasound and protein immunodetection and the timely diagnosis, BC mortality rates have decreased in the last years in developed countries due to the diversity of available treatments ranging from surgery to chemotherapy, radiotherapy, hormonal therapy to monoclonal antibodies, but the incidence rates continues to rise [1,2]. BC is constituted by multiple disease states with diverse molecular behavior, the variability of such characteristics allow researchers to apply omics technologies to investigate this pathology [3]. For example, when analyzing the proteomic level, differences are found in the mutations and expressions of several genes that are currently used in the BC clinic as biomarkers, such as estrogen and progesterone receptors (ER and PgR, respectively), human epidermal growth factor receptor 2 (Her-2) and nuclear protein Ki-67 who play a very important role in BC clinical decision-making in terms of recurrence, optimal treatment plan and mortality rates in patients [4].

Due to the development and application of multiple timely detection programs constituted by non-invasive methods, such as self-examination, clinical examination and mammography, that have improved and complemented the diagnosis by histopathological means and due to the therapeutic regimens that have been developed, mortality caused by this type of cancer as well as the progress to subsequent phases and metastases has been reduced, especially in developed countries [5,6].

ER, PgR, and Her-2 are the most used biomarkers when defining the best treatment for each type of tumor. Nevertheless, these genes are not among the most frequently mutated in breast cancer, but there are potential driver mutations, molecular signatures, and other diagnostic features that potentially can lead to a targeted therapy [7]. There is a growing need to improve the clinical results that are offered to patients with BC, since this condition leads to high mortality rate because the diagnosis is made in late and advanced stages and because there is no adequate range of non-invasive methods able to detect cancer at the early stages; therefore, developing biomarkers for the first phases of the disease could provide patients with a better prognosis and therefore a better response to treatment and prevent the progression of the disease [8]. In the past few years, metabolites have been proposed as BC markers, along with genes and proteins [9]. Metabolites are the result of the expression of various genes, RNA and proteins, so the concentration of these represents the last scale of changes that DNA undergoes or editions that the environment exerts in the genetic material, secondary to non-physiological events, such as the pathology itself, the consumption of medicaments, dietary and population features, among other causes [4].

The total amount of cells in the body share the majority of metabolic processes for their maintenance, such as the processes for catabolism of amino acids and those related to energy production, which are altered in cells with BC. Due to diverse genetic mutations and epigenetic changes, the cell breaks its homeostasis and enters into a state of uncontrolled proliferation, characterized by an unbalanced apoptosis, and dysregulation of its natural metabolic processes. Using metabolomics tools allows researchers and physicians to develop an approach that can be more tailored to the phenotype of each patient [10].

Metabolomics as Tool to Diagnose Breast Cancer

Cancer is known as a pathological condition with multiple biochemical and physiological changes, including metabolic alterations. The first metabolic alteration described in cancer was Warburg effect [11,12].

The importance of metabolism in cancer is such that even to date the activity of lactate dehydrogenase, a metabolic enzyme, is a critical parameter for the diagnosis of cancer [13]. Currently, the new available technologies and knowledge of metabolism have allowed the development of metabolomics assays that constitute new strategies for diagnosis and treatment. Particularly, in breast cancer the metabolism is affected, mainly the metabolism of lipid and aminoacids [14-20].

Current diagnostic biomarkers

It is known that there are precise differences between the metabolic profiles of normal and tumor breast tissues, which mainly depend on the activation of the oncogenes of each patient and they will normally vary, but patients with the same diagnosis will coincide in several metabolites and be significantly different from the healthy patients, so there is a need for a metabolic pathway-based diagnostic model [21-24].

The main current manner to predict the presence of BC by pathogenic germline mutations, is via the mutation of the BRCA1 and BRCA2 genes, that indicates a strong predisposition to hereditary breast and ovarian cancers [25-28].

Once the disease is present, the main manner to classify the cancer subtype, to establish its prognosis and to choose the best available treatment, is through the expression of other genes, such as ER, PgR, Her-2 and Ki-67, which have shown different alterations in the metabolic profile, giving rise to possible targets for timely diagnosis [29].

Research performed to find new biomarkers

Metabolic changes in breast cancer are an excellent approach for the development of new diagnostic strategies which also allow better treatment options. For example, the altered glutamine metabolism could indicate changes on glutamine transport. It has been reported that SLC38A5, a glutamine transporter, indicates aggressive BC [30]. Additionally, the glutamate-glutamine ratio has been associated to the condition of the estrogen receptor, which allows the enrichment of glutamate to be a possible diagnostic biomarker for BC [31].

Despite metabolic biomarkers constituting new promising non-invasive and cost-effective diagnostic tools, they possess various difficulties such as lack of consistency between the experimental protocols and biological variability in the exchange rate of metabolites. Given this observation, machine learning computational methods that integrate metabolites features into pathway features have been developed and applied to identify early breast cancer diagnostic biomarkers [23]. An ideal biomarker for any disease, needs to have a high specificity and sensitivity and the ability to detect the disease at an early stage. In this pursuit, several potential options have been proposed.

Several studies have suggested the potential use of amino acids in the early detection of BC such as valine, lysine, arginine [32], and significant changes in the profile of amino acid concentrations have

been found in cancer patients, even in patients on asymptomatic stages.

Different profiles in serum for targets such as choline, glutamate, glutamine beta-alanine or xanthine have been described, depending on the type of BC [26,33-35]. One of the most studied pathways is the glutamine pathway, which shows a significant inhibitory effect on highly aggressive breast cancer cells [36,37]. Other important potential target is the Inositol 1,4,5 triphosphate (IP3R) receptor, that has an important role in the disruption of cellular metabolism during disease changing cell bioenergetics including amino acid and glutamate metabolism [38].

The use of metformin is being studied as a coadjuvant in the treatment of BC, since high glucose and lipid levels in serum have been associated to a risk factor for BC and its progression, similar to the metabolic profile of diabetic patients, with resistance to carbohydrates or with metabolic syndrome [28,39].

In addition, metabolomics can also be used in patients with resistance to classic chemotherapeutic drugs [27], whereas neoadjuvant chemotherapy was created, with major dependent response to choline levels and some amino acids, such as Tau and Gly [40].

Role of Metabolomics on the Improvement of Current Anti-Cancer Therapies

Cancer is a multifactorial disease that cannot only be explained through a specific genetic mutation or a particular environmental change. And BC is not an exception of this statement. Therefore, there are new proposals for treatments, such as the use of nanoparticles. This kind of treatment possesses the issue of not being specific and reaching other non-cancerous tissues, affecting their metabolism [41] another option is the use of monoclonal antibodies, which are currently exploited such as trastuzumab, which is beneficial in Her-2 positive patients, since this growth factor is highly expressed in malignant cells, a trastuzumab-based combination therapy significantly reduces the risk of death by 20 percent in the 30 months following the first dose in patients with metastatic BC [42]. But the new omics approach is the future approach for better diagnosis and treatment of complex diseases such as BC. Although, products of the primary metabolism were considered until a few years ago as "passive" compounds that did not affect the physiology of the cells, it is known that they are involved in the regulation of most of the cellular processes from differentiation, proliferation, to cell death and consequently diseases processes [43-45].

However not only cellular processes are affected by metabolites, also gene expression and proteins translation are regulated by the amount of metabolites present in the cell [46-48].

Therefore, the novel field of pharmacometabolomics that combines metabolite profiling and chemical data contributes to determine the pharmacokinetic and pharmacodynamic behaviors of a specific drug in an individual subject. Pharmacometabolomics studies can also provide additional information regarding the toxicity and side effects of drugs. This valuable information can help physicians to predict the sensitivity of tumors to an antineoplastic drug and determine whether the treatment will be effective and toxic.

Doxorubicin and methacrylamide conjugates have been studied *in vitro* cell culture models, *in vivo*, orthotropic breast cancer models, protein expression and flow cytometry studies to evaluate the

biochemical pathways and their alterations during the administration of these drugs, finding increased apoptosis, reduced glycolysis, and reduced levels of phospholipids, also demonstrating efficacy and toxicity of both agents, optimization in their pharmacokinetics and bio distribution [49].

The taxanes, as microtubule-targeting agents like docetaxel and paclitaxel, are usually used as neoadjuvant or adjuvant with anthracyclines or as monotherapy, have been shown to have an effect on glycolysis, phospholipid metabolism, and glutathione metabolism leading to the regulation of the expression of serum metabolites in patients, with an effect depending on whether the dose was high or low, which reveals an evident therapeutic dependence on the dose-response variation [9,50].

Chemotherapy with Gemcitabine-carboplatin, which is effective mainly in metastatic BC and in patients with resistance to anthracyclines and taxanes has been shown to have a highly variable clinical outcome among individuals, so the formate and acetate seric levels have been proposed as potential predictive markers to predict if this treatment will have an adequate response to make the decision to administer this medication or not [51].

One of the most used therapeutic regimens in BC is trastuzumab-paclitaxel for Her-2 positive patients, where significant changes were found in the concentrations of spermidine, tryptophan, propylcarnitine and phosphatidylcholine diacyl phospholipids, where it was concluded that patients who showed high plasma concentrations of spermidine and lower concentrations of tryptophan will tend to be more benefited with this neoadjuvant treatment [26].

Unlike immunotherapy, current chemotherapeutic treatments do not have biomarkers that can guide them to target only diseased cells. In order to benefit a greater proportion of cancer cells effectively and safely, and in order to reduce the variations among patients, there is a proposal to study endogenous metabolites to predict pharmacodynamics of chemotherapeutic drugs and offer a personalized treatment [52].

Even for molecularly targeted drugs, using genomic data as an indicator of treatment has limitations. Therefore, deep learning methods have been developed to still exploit integrative omics (genomics, metabolomics, etc.) data to train classifiers that can help predicting the effectiveness of drugs in cancer cells. This new method is the beginning of a huge effort to predict the efficacy of drugs, regardless of their specificity [53].

Metabolomics for Development of New Anti-Cancer Therapies

Because of the great variability and complexity in the patterns of cancer expression, the pathways of cellular metabolism have been studied, seeking alterations in the concentrations of different metabolites, to influence these pathways and in this way be able to offer options for new targets [54], such as described below.

Metabolic profiles to study metabolic differences

The tricarboxylic acid (TCA) cycle, which is involved in cell energy production, the macromolecules synthesis and the redox balance requirements, has been proposed as a possible and an attractive new target that is already being studied in clinical phases. The inhibition of glutaminolysis in the TCA cycle is mainly studied by means of depletion of glutamine in plasma (L-aspariginase) or blockade of

glutamine transport (sulfasalazine). Therefore, by understanding the tumorigenesis favored by the TCA cycle, the enzymes that are damaged by cancer metabolic and epigenetic changes could be inhibited in a timely and effective manner, principally succinate dehydrogenase, fumarate hydratase, and isocitrate dehydrogenase [55,56].

The lipidome is a biomarker dependent mainly on diet and acts as a result of physiologic changes. Metabolic profile and dietary exposures are closely related to the predisposition to various types of cancer [57]. In the case of BC, it has been observed that an elevation in monounsaturated lipids and a low ratio between n-6 and n-3 fatty acids present a possibility to reduce the risk of developing BC, especially in pre-menopausal women, particularly for ER+ breast cancer. On the other hand, it is observed that high concentrations of lysophospholipids have been found related to the development and progression of more aggressive cancer [15]. Thus, the study of the lipid profile may help in the prevention of BC and in classifying its malignancy differentiation and metastatic potential [58,59].

The metabolic pathway of Choline is involved in functions like cell signaling, lipid metabolism, and membrane integrity. It is reported that metabolites, as phosphocholine have been found in high concentrations in patients with cancer, in comparison with healthy patients; whereas high concentrations of total choline levels have been related to the malignancy degree of the neoplasm [60].

Racial features also have an important role in the metabolic profile, since African-American women express different patterns than Caucasian women. For example, African-American women expressed higher levels of glutathione, choline and glutamine, and therefore, increased activation of pathways associated with energy metabolism, which was demonstrated at lower levels of ATP in triple-negative breast cancer (TNBC) compared with Luminal A breast cancer; whereas in Caucasian women, an increase in the pyrimidine synthesis of the pentose phosphate pathway has been observed and this expression promoted resistance to chemotherapy in TNBC and it is normally found with an anaplastic pyruvate carboxylation, this constitutes a possible therapeutic option for this type of patients [61]. Metabolic profiles of triple negative and luminal A breast cancer subtypes in African Americans were correlated to key metabolic differences [61,62].

Conclusions

The field of metabolomics has a vast potential for developing a more realistic personalized medicine approach, specifically in the field of oncology, where there is an enormous need for tailored and more effective treatments. The advantage of metabolomics compared to other omics technologies is evident since the metabolic profile of a patient in response to a certain drug can give us the tools to prescribe the most optimal drug for a cancer patient with a specific pathological status that is directly related to their metabolic map.

This metabolic map constitutes also a necessary tool to identify metabolites delivered and produced in concentrations different to the physiological normal levels and that are an indication of non-regulated biological pathways as a result of cancer effects. Such metabolites could comprise new therapeutic targets that could be researched to create new anti-cancer drugs (Figure 1).

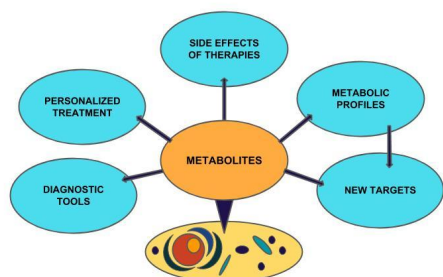


Figure 1: Applications of the metabolic profile. Metabolites, as a result of the expression of genes related to cellular metabolism, can be used for the development of various treatment tools based on new targets in order to offer the patient a personalized treatment and thus reduce side effects of the therapies and have a better clinical outcome.

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