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OMICS: A NEW VISION FOR BREAST CANCER TREATMENT

OMICS: UNA NUEVA VISIÓN DEL TRATAMIENTO DEL CÁNCER DE MAMA

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ABSTRACT

Breast cancer is an extremely heterogeneous disease with diverse morphologies, molecular characteristics, and clinical behaviour whose causes include interactions of both genetic and environmental factors. Currently, more than 2,261,419 cases and 684,996 deaths are reported each year worldwide and although great strides have been made, available treatments are inadequate for its most intractable forms. Therefore, knowing the associated molecular bases is essential to improve the prognosis and survival. The omics are high performance technologies utilized to quantify cellular components at a large scale. In this regard, this article presents genomic, epigenomic, transcriptomic, and proteomic research on breast cancer, in an attempt to understand and identify potential therapeutic molecular targets.

Key words: breast cancer, genomics, epigenomics, nutrigenomics, transcriptomics, proteomics, metabolomics.

RESUMEN

El cáncer de mama es una enfermedad extremadamente heterogénea con diversas morfologías, características moleculares, y comportamiento clínico, cuyas causas incluyen interacciones tanto de factores genéticos como ambientales. Actualmente, se reportan más de 2,261,419 casos y 684,996 muertes cada año en todo el mundo y, aunque se han realizado grandes avances, los tratamientos disponibles son inadecuados para sus formas más intratables. Por tanto, conocer las bases moleculares asociadas es imprescindible para mejorar el pronóstico y la supervivencia. Las ómicas son tecnologías de alto rendimiento, utilizadas para cuantificar componentes celulares a gran escala. En ese sentido, este artículo expone investigaciones genómicas, epigenómicas, transcriptómicas, y proteómicas sobre el cáncer de mama, en un intento por comprender e identificar posibles blancos moleculares terapéuticos.

Palabras clave: cáncer de mama, genómica, epigenómica, nutrigenómica, transcriptómica, proteómica, metabolómica.

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INTRODUCTION

Breast cancer is one of the most common women's cancers with more than 2,261,419 cases and 684,996 deaths each year worldwide, representing 15.5% of all female deaths (Global Cancer Observatory, 2023). The incidence of breast cancer is increasing in the developing world due to increased life expectancy, increased urbanization and the adoption of western lifestyles (Sauter, 2018).

This disease is categorized into three basic therapeutic groups: the estrogen receptor (ER) positive group, HER2 (also called ERBB2) group, and the basal-like breast cancer which is characterized by the lack of expression of ER, progesterone receptor and HER2 (Koboldt *et al.*, 2012). It is an extremely heterogeneous disease with diverse morphologies, molecular characteristics and clinical behavior caused by the interaction of both genetic and environmental risk factors (Guo *et al.*, 2018). Although advances in the understanding of this disease have been made in the last decade, the available treatments remain inadequate, particularly for the most intractable forms of breast cancer.

Omics are technologies used to quantify cellular components on a large scale. The potential benefit in cancer research is promising, since they offer an unmatched opportunity to define cancer at both pathological and molecular levels (Orsini *et al.*, 2023). This article aims to present research based on the gene (genomics)-DNA (epigenomics)-RNA (transcriptomics)-protein (proteomics) dogma (Figure 1), which allows us to understand the molecular mechanisms associated with the pathogenesis of breast cancer, in order to identify new molecular targets for therapeutic intervention.

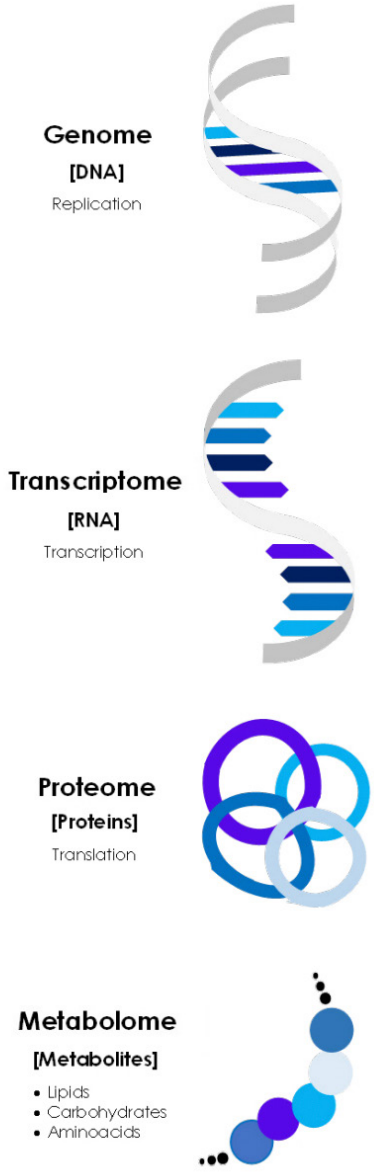

Figure 1. Omics family.

METHODS

In this article, required information was collected through literature review and keyword query (breast cancer, cancer, biomarkers, genomic, personalized medicine, pharmacogenomic, epigenomic, nutrigenomic, personalized diet, carcinogenic food, transcriptomic and proteomic) in credible scientific websites such as, Google Scholar, Scientific Electronic Library Online (SciELO), Medline, and the search engine for electronic journals and books of Universidad Nacional de Colombia and Universidad Autónoma de Barcelona.

Genomics

Genomics is the comprehensive analysis of genes, their DNA structure and their function. Genome analysis has improved our understanding of the mechanisms of breast cancer, thanks to the rapid progress in molecular biology and genome sciences in the past decades, expanding our knowledge at the cellular, molecular and genomic levels (Feng *et al.*, 2018).

The main goal of cancer sequencing studies is to identify genes that have undergone somatic mutations, contributing to malignant transformation (Goncalves *et al.*, 2014). The Cancer Genome Atlas researchers obtained tumor and germline DNA samples from 825 patients who presented breast cancer and found 30,626 somatic mutations which included 28,319 point mutations, four dinucleotide mutations, and 2,302 insertions/deletions (Koboldt *et al.*, 2012). These researchers identified all

genes previously found to be implicated in breast cancer (*PIK3CA*, *PTEN*, *AKT1*, *TP53*, *GATA3*, *CDH1*, *RB1*, *MLL3*, *MAP3K1* and *CDKN1B*) and, furthermore, they found 26 novel significant mutated genes. Also, germline variants were identified in *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *NBN*, *PTEN*, *RAD51C* and *TP53* genes (Koboldt *et al.*, 2012) which could be potential biomarkers in breast cancer. Of these genes, *BRCA1* and *BRCA2* are likely to be the main genes involved breast cancer. Impairment or loss of function of one of these two genes is involved in substantial genome instability, including increased number of mutations, DNA breakage and chromatid exchanges, increased sensitivity to DNA damage, and defects in cell cycle checkpoint functions (Barh, 2014).

Currently, there are a variety of risk assessment tools that provide information on breast cancer gene mutation status, prior to the development of the disease. These findings allow the implementation of prevention strategies, such as the use of chemoprevention medications (tamoxifen and raloxifene) (Abreu *et al.*, 2014; Sauter, 2018), or mastectomy which is a reasonable approach for women without breast cancer who have a known deleterious mutation in *BRCA1*, *BRCA2*, *TP53*, *PALB2*, *CDH1*, or *PTEN* (Bertier *et al.*, 2016).

On the other hand, the identification of those mutated genes, which are not present in the normal cells of the organism, would allow the pharmaceutical industry to find potential therapeutic targets for cancer cells, reducing the incidence of adverse reactions and thus improving the adherence to treatments.

Through pharmacogenomic studies it has been possible to identify that gene variation in drug metabolizing enzymes, drug transporters and drug targets alter the therapeutic outcome of the anti-cancer drugs (Hossain *et al.*, 2017). For example, tamoxifen is required to be metabolized into endoxifen via *CYP2D6* before it can exhibit its effects, for this reason individuals with polymorphism in *CYP2D6* exhibit considerable variability in the effect of this medication (Chan *et al.*, 2017). On the other hand, Irinotecan is also a pro-drug and should be converted to its active metabolite, SN-38, which is then metabolized by the UGT1A1 enzyme for further excretion, however patients with UGT1A1*28 genotype have a risk factor for severe neutropenia due to accumulation of this metabolite (Hossain *et al.*, 2017).

Finally, the study of mutations associated with therapy resistance has been another important application of genomics. For example, Razavi *et al.* (2018) investigated associations between genomic aberrations and response to therapy in 1,501 breast tissue samples (HR+HER2) and they found that *ESR1*, *ERBB2* and *NF1* were the genes most commonly associated with endocrine resistant tumors.

Epigenomics

Epigenetics refers to the study of gene function and regulation alterations without changes in the DNA sequence of the genome. The main epigenetic modifications are DNA methylation, histone modifications and small noncoding RNAs (Ornellas *et al.*, 2017). Epigenomics is the study of the complete set of epigenetic modifications.

DNA methylation is the first epigenetic modification to be associated with cancer and the most widely studied. A methyl group is transferred by enzyme DNA-methyltransferase to the 5-position of cytosine. CpG islands are regions of DNA and constitute approximately 60% of the promoters of mammalian genes. In these regions there is a high concentration of cytosine and guanine pairs. Hypermethylation of CpG islands induces gene silencing as a result of blocking the binding site of transcription factors and the transcription machinery, it also functions as a binding site for repressive transcription complexes (Zhu *et al.*, 2005).

A family of proteins with a methyl-CpG-binding domain (MBDs) are strongly involved in the interpretation of information encoded by DNA methylation and recruitment of enzymes responsible for establishing a silence state of chromatin (Hendrich, 1998). For example, López-Serra and Esteller (2008) found in an *in vitro* assay that removal of MBDs results in a release of gene silencing associated with a loss of MBD occupancy in 5´-CpG islands, without any change in the DNA methylation pattern (Ballestar *et al.*, 2008).

In cancer, the promoter CpG islands of many tumor suppressor genes become hypermethylated affecting cell cycle, apoptosis, cell adherence and DNA repair (López-Serra and Esteller, 2008). For example, genes such as *p16*, *ink4a*, *hMLH1* and *BRCA1* are silenced in many types of cancer. Specifically, hypermethylation of the *BRCA1* CpG island occurs mainly in breast and ovarian cancer (Esteller, 2008).

Histones are nuclear proteins associated with DNA molecules which are positively charged at physiological pH (Pasculli *et al.*, 2018). Histone acetylation is a reversible reaction consisting in addition of an acetyl group to an amino acid residue. The enzymes which catalyse these reactions are the histone acetyltransferases (HAT) and the histone deacetylase (HDAC). The acetylation of histones by HAT neutralizes their positive charge, reducing the affinity of the histone tail with negatively charged DNA. As a result, chromatin adopts a more relaxed structure, enabling the recruitment of the transcriptional machinery. This reaction is reversed by HDACs (Hyun-Jung and Suk-Chul, 2011).

The role of histone acetylation in breast cancer has been strongly studied and it has been found that it

promotes the expression of certain genes, which can cause breast cancer. P300 is a HAT which leads to some gene activation including several oncogenic. Heightened *p300* expression has been observed in primary human breast cancers (Guo *et al.*, 2018). On the other hand, it has been found that in normal breast tissue, the expression of some HDAC, such as SIRT1, is significantly lower than in breast cancer tissue and, for this reason, this enzyme has been associated with the development of breast cancer (Guo *et al.*, 2018).

Another important histone modification is methylation, which takes place at lysine and arginine residues and is carried out by histone methyltransferases (HMTs) which transfer a methyl group to these amino acids (Tryndyak *et al.*, 2006). This epigenetic modification plays an important role in chromatin remodeling and transcriptional activity, with activation or repression of transcription, depending on the position of methylation (Dumitrescu, 2012).

Changes in histone marks have been associated with malignant transformation and metastatic behavior in *in vitro* studies. For example, an increase in histones H3K9me3 (associated with compacted chromatin) was observed in the triple negative breast cancer, suggesting that it may be linked to an increased metastatic potential. In addition, LSD1 (Lysine-specific histone demethylase) is highly expressed in estrogen receptor negative breast cancer and was associated with a more aggressive behavior (Pasculli *et al.*, 2018).

MicroRNAs (miRNAs) are small noncoding RNAs which usually have 20–25 nucleotides. They are transcribed by RNA polymerase II and act by repressing gene expression by binding to regions of a target messenger RNA. Recent studies show that some miRNAs regulate cell proliferation and apoptosis processes that are important in cancer formation. Furthermore, overexpressed miRNAs in cancers may function as oncogenes and promote cancer development by negatively regulating tumor suppressor genes that control cell differentiation or apoptosis (Rufino-Palomares *et al*, 2013; Zhang *et al.*, 2017). Several investigations regarding to miRNA profiling has led to the identification of changes in miRNAs expression levels in human breast cancer (Zhang *et al.*, 2017).

The extensive and frequent hypermethylation of miRNA genes in human breast cancer supports the concept that epigenetic instability is an important early event in human tumorigenesis. Considering the presence of miRNA gene hypermethylation in breast cancer, it could serve as an epigenetic marker (Saito *et al.*, 2006; Tang *et al.*, 2017).

Nutrigenomics

Nutrigenomics relates the genomic and nutrition of a person. Thereby, ingested food can modify the gene expression patterns, resulting in potential benefits or adverse effects in the health of individuals (Kohlmeier *et al.*, 2016).

Inherited cancers through a germinal line represent 5% of the total cases, the remaining 95% originate sporadically from exposure to environmental factors. In breast cancer only between 5 and 10% of the cases correspond to some inherited susceptibility, thus food habits are considered a potential constituent within environmental factors (Mathers, 2004).

There are several studies that relate breast cancer with nutrition, but these are not conclusive due to the molecular complexity involved and the large number of components contained in diets. Moreover, bioactive food compounds can interact with genes affecting transcription factors, protein expression and metabolite production (García *et al.*, 2010). Research supports the fact that the absence of intake of natural protective components may be associated with carcinogenic diseases (Ross, 2007; Bissoondath *et al.*, 2018).

Studies on sporadic breast cancers have shown that bioactive components present in fruits and vegetables can prevent carcinogenesis by several mechanisms, such as blocking metabolic activation by increasing detoxification. Some examples of these natural compounds with inhibitory effects on tumorigenesis include isothiocyanates, catechins, resveratrol, curcuminoids, procyanidins, isoflavones and antioxidant vitamins (Keum *et al.*, 2004). On the other hand, it has also been reported that the high consumption of meats and saturated fatty acids is associated with an increased breast cancer risk (Ross, 2007; Bissonauth *et al.*, 2008).

These studies also stand out benefits of vitamin E, which presents chemopreventive effects on breast epithelial cells, including inhibition of growth, differentiation and protection against various cellular stresses. Soy intake has shown a lower risk of cancer in women who have consumed it during puberty, compared to women living in Western and Asian low-consumption countries (Lee *et al.*, 2009).

In the same sense, daidzein (isoflavone present in soy) has been shown to inhibit the growth of cancer cells, inhibiting cell migration and invasion induced by TNF-α (tumor necrosis factor) in human breast cancer cells (Ramasamy *et al.*, 2017). Another isoflavone, genistein, is associated with increased expression of breast tumor suppressors PTEN and E-cadherin, thus genistein treatment for BRCA1 succeeds in silencing breast cancer cells. Additionally, its inhibitory action on estrogen receptors and its associated vascular endothelial growth

factor (VEGFR) has also been reported (Bhat *et al.*, 2021).

HER-2 is expressed in breast cancer, receiving much attention from anti-HER-2 monoclonal antibodies (trastuzumab). The accessibility of its extracellular domain makes it ideal for the delivery of antitumor drugs, which is why several artificial ligands targeting HER-2 have been developed (Tai *et al.*, 2010). In addition, gamma linolenic acid (GLA) is an essential type of omega-6 fat that can inhibit the action of the *HER-2* cancer gene. Therefore, it is proposed as a valuable therapy against breast cancer, especially for its selective antitumor properties (Kenny *et al.*, 2000).

On the other hand, there is enough scientific evidence that alcoholic drinks are a carcinogenic agent and have been classified as group 1 (highly carcinogenic) by the International Agency for Research on Cancer. Furthermore, they have been responsible of, among many other diseases, breast cancer in women (Carcinogenic Risks to Humans, 2007).

Finally, it is necessary to mention that several bioactive compounds of food can control the patterns of gene expression and that their influence on the transcription and translation of genes depends not only on the concentration but also on the time of consumption.

Transcriptomics

Transcription is the process of converting DNA to RNA. This RNA can follow different paths, such as being translated into peptides to be used as a guide for protein synthesis or assist in gene regulation and enzymatic activity of cells. Transcriptome, by definition, is the collection of all RNA in a cell, and transcriptomics is the examination of these RNA. Transcriptome has various types of RNA, such as mRNA, non-coding RNA (which became a hot spot for breast cancer research in the past) (Shi *et al.*, 2017) and small RNA. Long non-coding RNAs are also thought to be involved in many diseases, including breast cancer (Liu *et al.*, 2016). Transcriptomic techniques help to profile, localize, and process transcriptomes, as well as to perform post-transcriptional modifications and decode RNA.

An important element for transcriptomic analysis of cancer is gene expression. This is the study of gene activity, going from DNA to proteins. Especially, the oncogene analysis is very useful in understanding the processes that drive cancer. Generally, the use of cDNA libraries and oligonucleotide microarrays allow the study of oncogenes.

cDNA is a type of DNA obtained using extracted mRNA as a template. This process requires reverse transcriptase enzymes (Hawkins *et al.*, 2003). These DNA are complementary to mRNA fragments and are used to study gene expression through a solid surface, in a process called hybridization. This process involves attachment of cDNA to specific locations that match with their respective mRNA. If mRNA is fluorescently labeled, it is possible to measure different intensities from each location. cDNA sequencing is used in obtaining quantitative gene expression, which in turn helps to identify 'malfunctioning' genes in various pathological states (Wanling *et al.* 2009).

Oligonucleotide microarrays are utilized to obtain better hybridization results, by using synthetically created DNA. With this process, it was determined that there are two overexpressed genes related to breast cancer: histone *H2AFJ*, that makes up the nucleosome and plays a central role in the control of DNA transcription (Rendon *et al.*, 2021) and epidermal growth factor receptor kinase substrate 8 *(EPS8*), that participates in the signaling pathway of the epidermal growth factor receptor (*EGFR*) (Chen *et al.*, 2015). As the results show, cDNA arrays are useful to identify any possible problem related to breast cancer.

In addition, with genomic techniques such as microarrays, next-generation sequencing and whole-exome sequencing, breast cancer diagnosis is going through a significant evolution. Molecular diagnostic assays, such as MammaPrint® or Oncotype DX®, allow to identify genetic mutations (Abreu *et al.*, 2014). Companies such as Exact Sciences (2018) offer the Oncotype DX breast cancer test which examines the activity of 21 genes in the patient's breast tumor tissue in order to provide an accurately diagnosis. Once the mutations in the patient's tumor genome have been identified, the next step is to find those that are targetable by a therapeutic agent (Sauter, 2018; Abreu *et al.*, 2014). This information could be obtained with the use of pharmGKB, an online resource that provides a list of most, if not all, pharmacogenomics agents approved or under consideration by the FDA, EMA, and others (Bertier *et al.*, 2016). On the other hand, Mamma Print examines the expression of 70 genes linked to different pathways of control of apoptosis, being recommended as a predictive tool for chemotherapy by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) (Zeng ans Zhang, 2022).

Furthermore, RNA-sequencing is one of the next generation sequencing techniques. This process involves creating cDNA libraries from known RNA sequences. These cDNA are studied and classified. According to Kuo-Hua *et al.* (2018), this method can have advantages over microarrays, as it has an expansive coverage, which allows study of novel coding and non-coding transcripts. These cDNA fragments can be either compared with reference sequences or reassembled to find out the

whole RNA sequence.

On the other hand, gene expression profile has been useful for classifying breast cancers into subgroups. After analyzing 85 tissue samples, Sorlie *et al.* (2001) suggested that breast cancer could be subdivided into: (1) luminal and its subtypes: A estrogen receptors, B progesterone receptors, C the type of treatment that corresponds will depend on the luminal subtype, and (2) estrogen receptor positive group (ER+), HER2 positive (Her2+) and Triple-negative breast cancer (TNBC). The latter is subdivided into six subtypes, displaying unique gene expression and ontologies, including two basal-like (BL1 and BL2), one immunomodulatory (IM), one mesenchymal (M), one mesenchymal stem-like (MSL), and one luminal androgen receptor (LAR) subtype (Lehmann *et al.*, 2011). However, there are other TNBC classifications: luminal androgen receptor (AR; LAR), mesenchymal (MES), basal-like immunosuppressed (BLIS), and basal-like immune-activated (BLIA) (Burstein *et al.*, 2015). This has made the classification of breast cancer more complex, but it has also opened up new lines of research and treatment.

Proteomics

Cells contain the same genome, but they express different proteins responding to a specific micro-environment. The function of proteins depends on their correct amino acid sequence, their post-translational modifications, their three-dimensional structure, their concentration, their interactions with other proteins and the extracellular environment. These characteristics make their experimental analysis difficult (Pando-Robles and Lanz-Mendoza, 2009). Cancer-relevant proteomics is based on finding differentially expressed protein markers in tumors and new therapeutic targets.

Different methodologies can be combined in proteomic studies. The most commonly used methods involve protein extraction from the sample, separation by one-dimensional (1-D) or two-dimensional (2-D) electrophoresis or liquid chromatography, ionization through Matrix-Assisted Laser Desorption/Ionization or Electrospray Ionization (Barbosa *et al.*, 2012), fragmentation, peptide analysis and detection through techniques such as mass spectrometry or nuclear magnetic resonance (Qingjun *et al.*, 2016), and data analysis.

In a recent study, researchers quantified by high-resolution mass spectrometry more than 12,000 proteins and 33,000 phosphorylation sites and performed an atypical analysis of the phosphorylation states of the kinase enzyme. They found aberrantly activated kinases in breast cancer samples, such as HER2, CDK12, PAK1, PTK2, RIPK2, and TLK2. With these results, scientists hope to identify more druggable kinase proteins, in addition to HER2, which can be targeted with trastuzumab (National Cancer Institute, 2018).

Other researchers analyzed the proteome of triple-negative breast cancer and found six kinases that, when inhibited by drug combinations, achieved a survival rate greater than 93% (Zagorac *et al.*, 2018). In this way it is evident that through the methods of proteomics it is possible to identify potential therapeutic targets in the treatment of breast cancer.

In addition, through proteomic methods it is possible to find novel biomarkers for risk assessment, screening, early diagnosis and monitoring breast cancer progression. For example, it is possible to identify proteins secreted from cancer cells in response to the tumorigenic process in serum or plasma (Mardamshina and Geiger, 2017). The risk of breast cancer recurrence can be tested through the use of serum tumor markers such as carcinoembryonic antigen (CEA) and Ca 15.3 (MUC-1 mucin glycoproteins) (Drake *et al.*, 2011) which are increased before symptoms or clinical signs appear. Particularly, CEA is a non-specific serum biomarker that is elevated in various malignancies such as breast cancer (Kankanala and Mukkamalla, 2023)

In general, through proteogenomic analysis of breast cancer it is possible to elucidate the functional consequences of somatic mutations, to narrow candidate nominations for driver genes within large deletions and amplified regions, and to identify therapeutic targets (Mertins *et al.*, 2016).

Metabolomics

The message in an organism's DNA (genome) is transcribed into RNA (transcriptome), which is translated into proteins (proteome), participating in the formation of small molecules known as metabolites. Therefore, alterations in the genes could cause changes in the metabolic profile, which can facilitate the development of cancer (Subramani, 2022).

Thus, metabolomics studies focused on the analysis of metabolites, offer information on the changes that occur during the development and progression of cancer, through the identification of biomarkers, that can even be used as therapeutic targets (Hart *et al.*, 2016).

The assessment of metabolites can be carried out using techniques such as: gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectometry (LC-MS) and nuclear magnetic resonance spectroscopy (NMR) (Alakwaa *et al.*, 2018). These techniques are used to identify metabolites, which will be correlated with a certain phenotype (physiological or alteration). In this task it is feasible to use databases that allow a better correlation.

The metabolome of cancer is made up of both oncological metabolites and those that arise from the body's systemic response. In particular, cancer cells need abnormal growth and proliferation rates, which require supplements of metabolic precursors for proliferation, angiogenesis, epithelial transition to mesenchyma and even mitochondrial metabolism (Subramani, 2022).

In breast cancer, more than 30 endogenous metabolites are identified in the breast tissue, which include: elevated choline, glycerophosphatcholine, low glucose and lactate increase (Aboud and Weiss, 2013), as well as alterations in glutamine levels (Alakwaa *et al.*, 2018), lipids and serine (Mikó *et al.*, 2019).

Particularities are also found in (1) carbohydrates: metabolites such as ATP, acetyl-coA and NAD regulate post-translational modifications that negatively affect protein activity and counteract normal biological pathways (Fuchinoue et al., 2015). (2) lipids: increased cell growth and tumor formation require increased lipid synthesis and absorption, so lipogenesis is essential in tumor growth (Eghlimi et al., 2020). (3) amino acids: the metabolism of glutamine (its derivatives: citrate, fumarate and malate), Na+-dependent transporters, the amino acid transport system (alanine, serine and cysteine), are associated with oxidative damage and overproduction of free radicals associated with genetic diseases (Subramani, 2022). In sum, the consumption and use of carbohydrates, lipids and amino acids help to maintain the growth of cancer cells.

Metabolomics provides knowledge of the dynamic changes that occur in cancer cells, in order to identify early biomarkers that can allow sensitive and specific detection for breast cancer diagnosis (Jasbi *et al.*, 2019). However, there are numerous challenges in the extraction and identification of metabolites, so it is still an emerging field.

CONCLUSIONS

Omics are high-throughput technologies which, given its versatility and integrity, have allowed to offer a new perspective in the understanding of the molecular mechanisms that govern the susceptibility, occurrence and progression of breast cancer. Among the most important applications of these technologies is the identification of potential biomarkers, which could be aberrant genes, modified proteins, epigenetic alterations or oligonucleotide RNA chains that are expressed in cancer cells but not in normal cells. Using these biomarkers, we can implement prevention strategies, making an early diagnosis of the disease, identifying potential therapeutic targets in order to achieve more effective treatments than conventional therapies and studying the mutations involved in drug resistance. Finally, using these technologies we can study the contribution of external factors (such as diet) in epigenetic modifications which could increase our susceptibility to develop breast cancer. In any case, much of the treatment is based on specific molecular targets and inhibitors of DNA signaling or repair pathways, with chemotherapy being a conventional complementary treatment.

AUTHOR CONTRIBUTIONS

All the authors listed above have made substantial, direct, and intellectual contributions to the work and have approved it for publication.

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The authors declare not to have any conflict of interest.

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