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The Epigenetics in Breast Cancer: Review of its Pathogenic Implications and Projection in the Clinical Area

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Introduction

Breast cancer is a public health problem among women globally; Considering both sexes, it is estimated that breast cancer represents 27% of new diagnoses of cancer and 15% of deaths from cancer [1]. Since cancer is a genetic disease, the best way to understand it is through the study of the alterations in Deoxyribonucleic Acid (DNA) that led to its development. The concepts of epigenetics, micro-Ribonucleic Acid (RNA) and gene expression analysis are the product of new biological discoveries, have profoundly modified the understanding of the pathogenesis of breast cancer and have been the basis of the development of novel technologies [2]. The objective of this review is to contextualize the importance of breast cancer as a health problem and priority in clinical research, as well as to address the panorama of epigenetics in the genesis of this disease and its prognostic and therapeutic implications.

Epidemiology

Globally, breast cancer represents the first malignant cancer in incidence and the leading cause of cancer death among women (25.1% of cancer incidence, 14.7% of cancer mortality, and 5-year prevalence of 36.3% in 2012). Considering both sexes, it is positioned as the second malignant neoplasm in incidence and the fifth cause of cancer death (11.9% of cancer incidence, 6.4% of cancer mortality and 5-year prevalence of 19.2% in 2012). It represents the leading cause of cancer death in developing countries (14.3%) and the second in developed countries (15.4%). It is estimated that 1 in 8 women in the United States of America will develop breast cancer throughout their lifetime and is recognized as the leading cause of cancer death in women aged 20-59 [3]. Breast cancer is rare among men [1]. For Mexican women, it represents the first malignant neoplasm in incidence (24.8% of cancer incidence, 5-year prevalence of 34.3%) and the leading cause of cancer death (14.2% of cancer deaths). In statistics for both sexes, breast cancer has the highest incidence (20,444 cases in 2012, 13.8% of cancer diagnoses, 5-year prevalence of 21.1%) and the second place in cancer mortality (7.2% of deaths due to cancer). [4,5]. According to the latest data from the Histopathological Registry of Malignant Neoplasms, in 2006 there were 15433 new cases of breast cancer, most of them in the 40- to 59-years-old and ≥70-years-old, same as the one found in 2003. This means that in 2003 the National Health System institutions diagnosed more than 50 cases of breast cancer on each working day, most of which were discovered in advanced stages [6,7] The percentage of diagnoses, according to the clinical stage, is the following: [3,8] Stages 0 and I, 7.4%. Stage II, 34.4%. Stages III and IV, 42.1%. Not classifiable, 16.1%.

Treatment

Treatment of breast cancer includes management of the local disease with surgery, radiation therapy or both; and the treatment of systemic disease with chemotherapy, endocrine therapy, biological therapy, or a combination of these [3,9-19].

Prognosis

Survival after diagnosis of breast cancer depends on eradication of the primary tumor and local-regional disease (particularly the axillary, internal mammary and supraclavicular lymph nodes) and successful treatment of systemic micro metastases. Although macroscopically metastatic disease is considered incurable, a good quality of life can be achieved for years, especially if it is confined to the bone [3,8,9,20-22]. Early stage disease has a better prognosis and requires less aggressive treatment, with a survival rate of 98%. Diagnosis in the presence of distant metastases reduces the survival rate to 27% [23].

Epigenetics

Breast cancer is characterized by its complexity and triggering by multiple factors that include genetic and epigenetic alterations. Detection of specific mutations for clinical application in breast cancer is problematic because of the wide variability in the localization of mutations in each gene with the ability to elicit the malignant phenotype. On the other hand, it has been observed that the epigenetic alterations have more uniform characteristics and a prevalence of approximately 95% of the tumors. It has recently been revealed that abnormal gene expression induced by epigenetic changes plays a critical role in the carcinogenesis of the human breast by affecting cell cycle regulation, apoptosis, and signal transduction. Frequent methylation of tumor suppressor genes in breast cancer makes it a potentially useful marker for the diagnosis of the disease [2,21,24-26] Table 1.

Colon cancer	CpG-island methylation
	Hypermethylation of miRNAs
	Global genomic hypomethylation
	Loss of imprinting of IGF2
	Mutations of histone modifiers
	Diminished monoacetylated and trimethylated forms of histone H4
Breast cancer	CpG-island hypermethylation
	Global genomic hypomethylation
Lung cancer	CpG-island hypermethylation
	Global genomic hypomethylation
	Genomic deletions of CBP and the chromatin-remodeling factor BRG1
Glioma	CpG-island hypermethylation
Leukemia	CpG-island hypermethylation
	Translocations of histone modifiers
Lymphoma	CpG-island hypermethylation
	Diminished monoacetylated and trimethylated forms of histone H4
Bladder cancer	CpG-island hypermethylation
	Hypermethylation of miRNAs
	Global genomic hypomethylation
Kidney cancer	CpG-island hypermethylation
	Global genomic hypomethylation
	Loss of imprinting of IGF2
Prostate cancer	CpG-island hypermethylation
	Gene amplification of polycomb histone methyltransferase EZH2
	Aberrant modification pattern of histones H3 and H4
Esophageal cancer	CpG-island hypermethylation
	Gene amplification of histone demethylase JMJD2C/GASC1
Gastric cancer	CpG-island hypermethylation
Liver cancer	CpG-island hypermethylation
	Global genomic hypomethylation
Ovarian cancer	CpG-island hypermethylation

Table 1: Overview of Epigenetic Aberrations among Different Tumor Types [24].

Aberrant Methylation of Tumor Suppressor Genes

Alterations of methylation have been recognized as one of the most frequent alterations in human cancer; In tumor cells, hypermethylation of promoter regions is often accompanied by global hypomethylation. Anomalous methylation phenomena can cause the silencing of tumor suppressor genes by involving their promoter regions. The effect of methylation of promoter regions on tumor suppressor genes unfolds an extensive range of proteins throughout cell cycle progression and tissue functional differentiation, silencing genes involved in cell cycle regulation, DNA repair, signal transduction pathways mediated by hormones and receptors, apoptosis, cell adhesion, angiogenesis, and other processes. Epigenetic changes can ultimately lead to chromosomal instability, accumulation of mutations in critical cell signaling pathways, and progression of breast carcinogenesis [2,24,26].

Abnormal Methylation as a Marker

Abnormal DNA methylation has the potential to function as a tumor marker in early diagnosis and progression assessment because it occurs as an early and common event in cancer, it is detectable between large amounts of normal DNA and the techniques are relatively simple, sensitive, fast, and radiation-free.

The determination of methylation patterns can also be used in the evaluation of risk groups and designation of prognostic groups, as well as in the evaluation of the eligibility for the use of targeted treatments. In the context of the specific application in breast cancer, promising results have been reported with the detection of methylated DNA in ductal fluid, breast tissue and blood [26].

TP53

TP53 tumor suppressor protein is involved in cell cycle regulation, DNA repair, senescence and apoptosis, differentiation and tissue development, and cancer prevention. Its contribution to the regulatory mechanisms of mitochondrial DNA transcription or replication and the maintenance of mitochondrial genomic stability through base cleavage repair have recently been identified. While the TP53 mutation is only reported in approximately 20% of breast adenocarcinomas after sequencing of exons 5-8, epigenetic altera-

tions in the P14ARF / MDM2 / TP53 pathway and the PTEN regulator can be found in 73% of the cases. Mitochondrial DNA shows somatic-type mutations in 36% of tumors and germ line in 91% of cases after analysis of the D-loop region. Currently available information suggests a bidirectional relationship between pathway TP53 dysfunction and mitochondrial DNA mutations. Determinations of the proportion of PTEN methylation and mitochondrial DNA depletion in serum could be established as prognostic and predictive markers [27].

APC, BIN1, BMP6, BRCA1, CST6, ESR-b, GSTP1, P16, P21 and TIMP3

Pathway analysis of these candidate genes has a spectrum in the essential processes for the understanding of breast carcinogenesis such as the cell cycle and DNA repair (BRCA1, P16 and P21), invasion and metastasis (CST6 and TIMP3), Cell Proliferation (ESR-b), Signal Transduction (APC, BIN1 and BMP6) and Cell Detoxification (GSTP1). The evaluation of the methylation profile of the APC, BIN1, BMP6, BRCA1, CST6, ESR-b, GSTP1, P16, P21 and TIMP3 promoter regions has demonstrated through mass spectrometry identification of higher levels of methylated free tumor DNA in the serum from breast cancer patients (compared to individuals without breast cancer), and a significant concordance between the methylation profiles of tumor tissue and serum in normal breast tissue discrimination. Tumor DNA detection in serum reaches sensitivity and specificity above 90% (it has been estimated that >90% of free circulating DNA is derived from tumor tissues, released by necrosis or apoptosis) [26].

The Therapeutic Target in Abnormally Methylated Promoters

Contrary to genetic changes in cancer, epigenetics can be reversed or even prevented by pharmacological demethylation by agents that deplete DNA methyltransferase upon incorporation into DNA during replication. The mechanism of action of these drugs gives them the potential of application in diseases such as myelodysplastic syndrome, mesothelioma, preleukemic disorders, breast cancer and nasopharyngeal carcinoma, among others.

EZH2 and EHMT2

Histone methyltransferases EZH2 and EHMT2 maintain histone repressor methylation of the chromatin under the H3K27me and H3K9me, respectively. Removal of one of the tags by specific inhibitors of each methyltransferase may not be sufficient to induce the expression of genes with multiple repressor tags. On the other hand, dual inhibition by blockade with Small Interference Ribonucleic Acid (SiRNA) or by pharmacological inhibition showed superior effectiveness than the inhibition of a single methyltransferase. In fact, the expression of some genes could only be re-induced by dual blockade [28].

The Deacetylation of Histones as a Therapeutic Target

In the specific context of breast cancer, histone-related epigenetic modifications (in conjunction with abnormal DNA methylation) have been implicated in the loss of estrogen receptor expression, causing resistance to anti-estrogen therapies. Pharmacological reversal of these alterations by histone deacetylase inhibitors and DNA methyltransferase inhibitors has been shown to induce the re-expression of functional estrogen receptor and to sensitize cells to tamoxifen treatment [2,24].

Gene Name	Reported Percentage of Methylation in Breast Cancer Cell Lines	Major Functions
APC	44%	Cell polarity, chromosome segregation
BIN1	100%	Apoptosis
BMP6	-	Regulation of TGFβ signaling pathway
BRCA1	-	Cell cycle regulation, DNA repair, transcription regulation, apoptosis
CST6	-	Inhibition of cysteine proteases activity
p16/CDKN2A	33%	Cell cycle arrest
TIMP3	29%	Metastasis, invasion

Table 2: Summary of Tumor Suppress or Genes Methylated in Breast Cancer (subject of study by the authors) [2].

Discussion

The mentioned characteristics confer to the study of the epigenetics a potential of application in the clinical practice in a broad spectrum of the natural history of breast cancer and the process of its multidisciplinary attention. Determination of epigenetic changes by detection of CpG islands from tumor suppressor gene promoter regions is likely to be related to specific clinical variables and has the potential to be used as a screening method through the study of circulating DNA released by tumor cells. Some cancer-specific methylation panels have been shown to be useful in risk assessment and establishment of a tumor phenotype prognosis. Finally, gene silencing mediated by DNA methylation can be pharmacologically reversed, conferring a potential utility as a therapeutic target [2,24,27]. The direction of research within epigenetics shows some favorable characteristics for the study and treatment of oncological diseases: The consideration of adverse effects is a transcendental topic in the development of new oncological treatments. Virtually zero effects of epigenetic drugs have been reported in normal cells [2]. Epigenetic agents show versatility

in their integration into therapeutic regimens in accordance with the results obtained with the concomitant use of hormonal agents, traditional cytotoxic agents, natural dietary ingredients, and other epigenetic drugs [2,26,29]. Many drugs with prolonged clinical use in other indications have been shown to have epigenetic effects applicable to oncological therapies (some examples are procaine, procainamide, hydralazine and valproic acid). Their integration into the treatment of cancer would allow for agents with no patent and a widely known toxicity profile, representing savings in terms of the costs of developing new molecules and in the latency of the availability of drugs during the preclinical and clinical study process [29-33]. Although it may appear that knowledge about the epigenetics of breast cancer adds a classification system to the knowledge required to approach this set of diseases, current evidence further suggests the tendency to integrate classification by methylation and acetylation patterns to the molecular classification system by presumed origins of the cells that make up the tumor. Tumors of the luminal A, luminal B, and basal-like subtypes show profiles of epigenetic alterations, whereas cancers of the ERBB2-enriched and normal-like subtypes are distributed among the patterns of the others. Tumors of the basal-like subtype have a significantly lower methylation ratio than that of luminal B tumors, suggesting a greater number of mutations in the development of basal-like subtypes [34]. The most striking results in the study of epigenetic alterations in different diseases have been obtained by the methodology of mass spectrometry (capable of evaluating bioactive molecules and their chemical modifications with a great versatility as to specimens and nature of the target molecules) [35]. For example, in addition to the evaluation of DNA methylation and acetylation profiles, the mass spectrometry methodology with collision-induced dissociation and time-of-flight platforms could assist in the early detection of triple negative breast cancer through the determination of transthyretin, haptoglobin and antitrypsin in serum [36].

Conclusion

In general, epigenetic studies would have the advantage (in clinical practice) of favoring the early detection of the disease and many of its biological features in tumors that still have low cellularity, although many of the technologies described in the study of DNA methylation still require the establishment of a standard quantification curve or perform with moderate accuracy. On the other hand, the technologies employed for the analysis of these methylation profiles still have limited accessibility in Mexico's public health institutions.

The validation of methylated DNA studies with a more easily accessible technology for clinical practice and research in oncology, rheumatology, and endocrinology, among other specialties in charge of the care of patients with diseases that have recently described pathogenic mechanisms related to epigenetic alterations.

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