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REVIEW ARTICLE

Triple negative breast cancer: Deciphering the biology and heterogeneity

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Abstract Triple negative breast cancer (TNBC) is a subtype of breast cancer (BC) with a heterogeneous nature that stains negatively for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER2) during immunohistochemistry. Approximately 15–20% of all cases of breast cancer are triple negative phenotypes. Compared to patients with hormone receptor-positive cancer, TNBC patients are typically younger (<50 years), African American, and have a high incidence of mutations in BRCA1/2 genes. To date, not a single targeted therapy has been approved for TNBC treatment, and cytotoxic chemotherapy remains as the standard systemic treatment, meaning that TNBC is an aggressive subtype of breast cancer with a poor prognosis. In this review, the literature search was done up to date on which gene expression profile of TNBC has been analyzed in order to identify the consensus on molecular mechanisms involved in carcinogenesis and/or the prognostic markers of the disease. In conclusion, these studies have reported that TNBC is composed of several clusters or genomic signatures as basal keratins. They have also reported on their proliferation, luminal/basal apocrine, regulatory interferon, immune cells/immunoglobulin related to stem cells, epithelial-mesenchymal, androgen receptor and angiogenesis. However, not all research groups have reported reproducible results. This confirms the heterogeneous nature of TNBC and the need for research on uniform selection criteria. However, these discoveries have led to the proposal of new treatments, such as the addition of platinum salts, new combinations of therapeutic agents, some targeted therapies such as PARP inhibitors, and PI3K and androgen antagonists. There is no doubt that a better understanding of the nature of TNBC will allow individualized and more effective therapies.

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Introduction

Breast cancer (BC) is the main cause of death by cancer among women, and represents 30% of all new cancer cases in the Caucasian population. A woman living in the United States has a 12.3% (1 in every 8) risk of being diagnosed with breast cancer.[1] According to the World Health Organization, 1.67 million new cases were registered worldwide in 2012.[2] In Mexico, BC is also the first place in malignant neoplasia incidence among women. It represents 11.34% of all cancer cases, with a global increase of approximately 1.5% annually. However, in emerging countries this increase is up to 5%.[3]

Despite having the same origin tissue, BC represents a heterogeneous cancer group with complex biological behavior and a great clinical variability. Over the last 10 years, extensive research at a molecular and genetic level has been conducted in order to sub-type these BCs. This has permitted the determination of clinical, pathological and molecular variables, to select treatment modalities and forecast, in some cases, the evolution of the disease at the moment of diagnosis.[4]

Breast cancer classification

In the traditional way the most important information that pathologists gave oncologists, respect to the classification of breast cancer, included the status of the nodules and tumor size, histological grade and standard immunohistochemistry tests (IHC) status of hormone receptors: estrogen receptor (ER) and progesterone receptor (PR) (Fig. 1).

Later on, in the era of trastuzumab, information on the amplification status of the human epidermal growth factor receptor 2 gene (HER2) became routine. Combining all these parameters, it was possible to classify patients as high or low risk. There were however a group of patients who were in an intermediate category that could not be classified between these two groups. Results showed that 15% of the patients classified as low risk had relapsed or died due to a very aggressive disease. And patients classified as high risk, surprisingly 10–15% had a favorable response. All those results led to the conclusion that the method of classification was not very appropriate.

Thus, based only on standard IHC directed at cellular markers that reflect the availability of targeted therapies, breast cancer can also be classified into three main groups: (a) homone sensitive (ER or PR positive), (b) HER2 positive, sensitive to trastuzumab or (c) triple negative breast cancer (TNBC), defined by the absence of ER, PR and HER2 amplification.[5–8]

No targeted treatment is available for TNBT and chemotherapy remains the best therapeutic option. However, in the case of recurrence or chemoresistance, therapeutic options are very limited.[9]

Subsequently, in the late 90s, when platforms for genomic studies were available, IHC methods coupled with complementary DNA (cDNA) microarray technology, allowed for a more extensive BC classification and were able to define four different BC subgroups, which differ in prognosis and targets: (a) luminal A – positive to ER and PR, negative to the amplification of HER2, with a low proliferation index (Ki-67 < 14%); (b) luminal B – ER positive, HER2 positive or negative, high proliferation index (Ki-67 > 14%), negative or low positive PR; (c) positive for HER2 – overexpressed or amplified HER2, negative ER and PR; (d) basal-like or TNBC, also defined by the absence of ER, PR and HER2 amplification. However, this last assumption is not strictly accurate due as not all basal-like tumors are completely TNBC.[10,11]

This classification is based on the consideration that there are two cell types in the mammary gland, luminal cells and basal cells. These two cell types can be differentiated by IHC tests as luminal cells, which express ER and PR and that

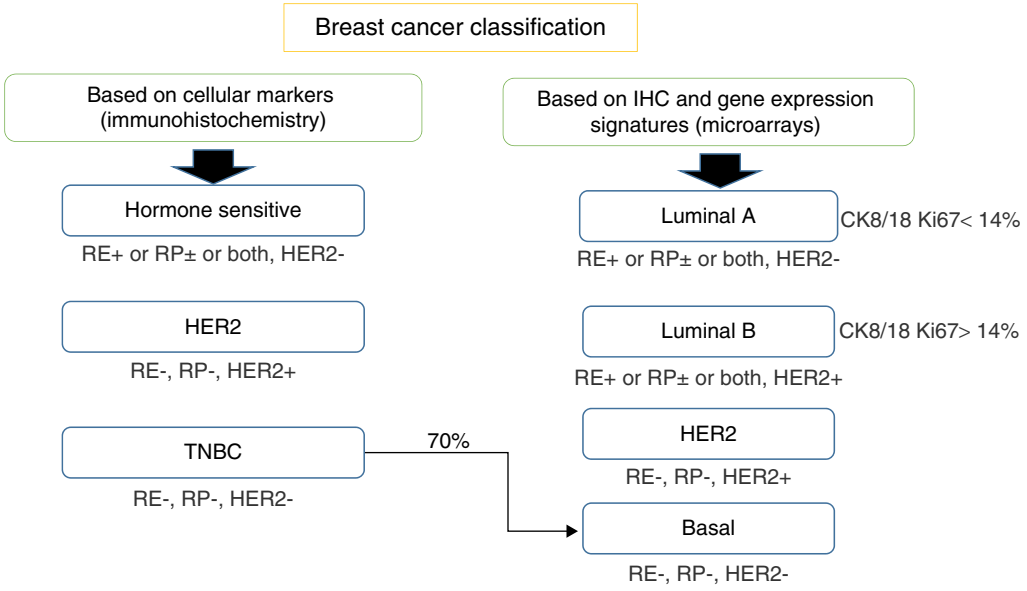

Figure 1 Breast cancer classification according to immunohistochemistry cellular markers (IHC) or according to a combination of IHC and microarray expression methods (gene signatures). ER, estrogen receptors; PR, progesterone receptors; HER2, epidermal growth receptor 2; CK, cytokeratin; EGFR, growth factor receptor.