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THE IMPORTANCE OF THE DIAGNOSIS OF THE ATM GENE (ATAXIA TELANGIECTASIA MUTATED) IN PATIENTS WITH HEREDITARY PRE-DISPOSITION TO BREAST CANCER; NARRATIVE LITERATURE REVIEW

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ABSTRACT

Breast cancer consists of a public health problem in Brazil, representing the first cause of cancer death in Brazilian women of all ages. The state of Rio Grande do Sul has one of the highest incidence and mortality rates in the country, and your capital, Porto Alegre, has the record Brazilian's city in new cases. This article discusses the importance of the research of the ATM gene (Ataxia Telangiectasia Mutated) in routine evaluations in patients with hereditary predisposition to breast cancer, diagnosed or not with the disease. The search was performed through the databases PubMed, SciELO and Science Direct, in which scientific articles were selected to explore the proposed theme, between the years of 2000 and 2017. The results indicate that the identification of individuals with dysfunctional ATM is relevant to determine etiological factors and to direct strategies for prevention, early diagnosis, besides supporting the medical team in the definition of the therapeutic protocol, with special attention to the radiosensitivity presented by these patients, whose ATM research may guide a targeted approach, with improvement in the quality of life and the prognosis of the patients.

KEYWORDS: Breast-cancer, Ataxia Telangiectasia Mutated, radiosensitivity.

INTRODUCTION

Breast cancer is a malignant tumor that starts in breast tissue cells. Considered the most common cancer type in the female population, in both developing and developed countries, has showed an exponential increase in new cases in recent years. However, mortality rates vary among different regions around the world, and are more significant in developed countries, with a prevalence of about 100 times greater in women than in men.[1] In Brazil these numbers are even more expressive, consisting of a serious public health problem, representing the first main cause of cancer death in Brazilian women of all ages.[2] Epidemiological data for the biennium 2016-2017 were estimated in about 58 thousand new cases of breast cancer in the country. Rio Grande do Sul, for unknown reasons, has one of the highest rates of breast cancer incidence and mortality in the country, being Porto Alegre the most important Brazilian city in these numbers.[3,4]

Breast cancer is a heterogeneous, multifactorial disease that involves genetic factors such as family history, high density of breast tissue, hormonal factors environmental such as lifestyle, sedentary lifestyle, obesity, alcohol consumption, smoking and exposure to ionizing radiation (IR). All these factors are seen as potential predisposing agents to the onset of breast cancer along with the natural aging of the body.[5]

In the last decades there has been an exponential increase in the understanding of the influence of the genetic factor on the individual risk of developing this type of cancer. Although most breast cancers are attributed to hereditary factors, a small portion has been referred for genetic profile research, with a higher prevalence of BRCA1 (BReastCAncerType 1) and BRCA2 (BReastCAncerType 2) genes.[5,6] Despite, many patients with a previous family history of breast cancer and under the age of 50 years may have a hereditary predisposition and do not present mutations in BRCA1 and BRCA2, but associated with lower penetrance, such as the ATM.[7-9]

ATM (11q22.3) is a recessive gene that encodes a protein kinase that plays a key role in the control of double-strand breakage (DSB) repair of DNA (Deoxyribonucleic Acid). In response to DNA damage repair (DDR) the ATM gene orchestrates the detection and repair of altered DNA, ensuring maintenance, gene stability, cell variability and homeostasis. In homozygous individuals, its dysfunction causes a disease

called A-T (Ataxia-Telangiectasia, ICD-10: G11.3). A-T is a rare autosomal and recessive genetic disorder that causes a combination of severe combined immunodeficiency (primarily affecting the humoral immune response) with progressive cerebellar ataxia. It is characterized by neurological signs, telangiectasia, increased susceptibility to infections and increased risk of cancer.[10,11] Heterozygous individuals are predisposed to immunodeficiency and are more likely to develop breast neoplasias, in addition to other pathologies such as myocardial infarction and chronic respiratory infections.[12] These individuals should not be exposed to exogenous agents that promote DNA damage, such as ionizing radiation, due to their deficiency in DNA repair, which may lead to the propagation of genetic error and to the susceptibility of the development of tumor cells.[11]

In this way, this article discusses the importance of ATM gene research in routine evaluations of patients with hereditary predisposition to breast cancer with young age ($\leq$ 50 years), diagnosed or not with the disease. The possibility of identifying individuals that are more susceptible to the development of breast cancer can determine etiological factors, prevention strategies, make early diagnosis possible or help to establish a therapeutic protocol that is more appropriate to the genetic profile of each patient, improving the quality of life and the prognosis.

MATERIAL AND METHODS

This study constitutes a descriptive narrative review on the most relevant aspects about the ATM gene, its role in DNA repair, its relation with a higher incidence of breast cancer, radiosensitivity and immunodeficiency. Data collection was performed between April and November 2017, and the databases of the Scientific Electronic Library Online (SciELO), National Library of Medicine (PubMed) and Science Direct were used for the research. The terms used in the electronic searches were "Ataxia-Telangiectasia (A-T)", "Ataxia Telangiectasia Mutated", "ATM", "breast cancer", "radiosensitivity", "immunodeficiency". In addition, an online survey was conducted using web search tools to consult documents of national and international agencies, such as the Ministry of Health (MS / Brazil), the National Cancer Institute (INCA), the National Agency of Sanitary Surveillance (ANVISA) American Society of Clinical Oncology (ASCO), American Cancer Society (ACS), National Comprehensive Cancer Network (NCCN), Ataxia Telangiectasia Children Project that could contribute data to compose this study.

The inclusion criteria were scientific articles that explored the proposed theme, published between the years 2000 and 2017. We excluded studies that did not have adequate bibliographic references, which were incomplete or with tertiary sources. In addition, it was decided not to include congresses's annals, theses, dissertations, monographs and books. Selected articles should be available in the form of original or review articles prioritizing primary references. The references of the selected articles were verified in order to identify other articles that met the inclusion criteria and that had not been located in the databases consulted. After the articles selection according to the eligibility criteria previously defined, the following steps were followed: exploratory reading, selective reading and choice of material that contemplated the objectives of this study, analysis of the texts and, finally, the performance of interpretive reading and writing.

RESULTS AND DISCUSSION

Currently the control of breast cancer is one of the priorities in the National Health Policy agenda in view of its magnitude as a public health problem in Brazil. Among the modalities of care foreseen for its control is early detection, which consists of diagnostic and tracing actions to subsidize the decision-making of managers in the Unified Health System (SUS) and guide the population. In this sense, the research of tumor markers can contribute to the better understanding of the genetic profile and establishment of the therapeutic conduct of each individual.

The American Society of Clinical Oncology (ASCO) recommends the use of tumor markers in the prevention, screening, treatment and surveillance of breast cancer.[12,13] In addition to these common markers, susceptibility genes research to breast cancer have been included in cases of breast cancer in patients with a family history of heredity and age young ($\leq$ 50 years),[12] high genes highlighting penetrance BRCA1 and BRCA2. However, other mutations of lesser penetrance, but high relevance, such as the ATM gene, are rarely included in genetic screening batteries and may be underdiagnosed.

The ATM protein is a protein belonging to the phosphatidylinositol-3-kinase family (PIKKs). It is an autosomal recessive hereditary gene, located on the long arm of chromosome 11, between positions 22 and 23 (11q22-23). The loss of its function in homozygous individuals leads to the development of A-T. In heterozygotes, it induces the susceptibility to some types of neoplasias, among them of the breast, as well as the disturbances of susceptibilities of the immune system.[14,15,16,17]

The ATM gene coordinates DNA repair by activating enzymes that are recognized and fixed as "damaged" or "broken", such as "undergoing changes by exogenous agents such as ionizing radiation and chemicals". Under normal conditions, when a DNA double-strand break occurs, the ATM is activated and recruited by the complex MRN (Nuclease Mre11), ATPase, RAD50 (RAD 50 recombinase and Nbs1 protein) pathways: (a) through its repair (b) through the passage of the cell cycle, (c) through chromosomal remodeling (d) through passage or cell death (Fig. 1). There is no DNA repair from the MRN complex and the genes BRCA1, RAD51 (RAD 51 recombination), RAD50 eTP53 (Tumor Protein

53) are activated. Motorcycle Proteins1 (SMC1) inhibitors of the cyclin A / CDK1 complex and CIP / KIP through the TP53 gene.[15]
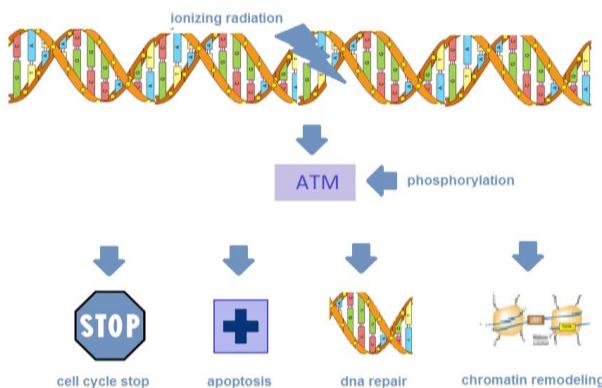

Fig. 1: ATM signaling network (Ataxia Telangiectasia Mutated) after breaking the double strand of DNA in the attempt of repair by the four routes.

In response to the activation of ATM, there is an increase in the activity of the TP53 gene, which by phosphorylation results in accumulation of this gene, with effectiveness in recruiting and activating other genes in the repair cascade.[18,19] Activation of ATM can induce the cells to block the cell cycle, and may occur in G1, S or G2 phases. This process can be mediated through the action of CHK2 (cyclin-dependent checkpoint kinase). The main checkpoint in G1 is the TP53 gene, in S o Cdc 25A and in G2 o Cdc 25C.[17] CHK2 can phosphorylate TP53 at serine 20, activating the checkpoint at G1. When damage lesions occur in G2 phase, the ATM-CHK2 pathway is activated and performs the blockade by Cdc25C phosphorylation (Fig. 2). Cycle blocking cell is an extremely important response because of the induced damage in the DNA. Interferences in this mechanism may result in accumulation and propagation of genetic alterations and/or uncontrolled cell growth, leading to genomic instability and neoplastic development.[17]
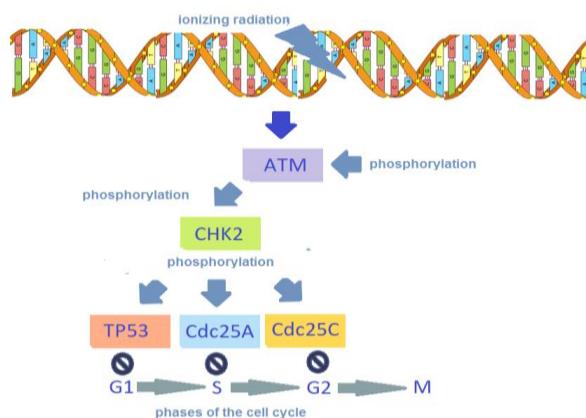

Fig. 2: ATM signaling pathway (Ataxia Telangiectasia Mutated) after induction of DNA damage. CHK2 (Checkpoint Kinase), TP53 (Tumor Protein 53); Cdc 25A and Cdc 25C (Cyclin Dependent Kinase).

In the last decades, great discoveries and identification of several genes directly involved in the heredity of cancers have led to the creation of Genetic Cancer Risk Assessment (GCRA) programs. These programs are performed largely in academic health centers, which aim to determine the risk of certain types of cancer, as well as diagnose and manage patients and families with hereditary syndromes.[4] Some tumor markers have been shown to be promising in predicting the progress of the disease and in the personalized therapeutic approach, being a valuable data source for disease monitoring, determining the prognosis and optimizing the treatment in a personalized way. Gene expression may help to measure the risk of recurrence and the cost-benefit ratio of radiotherapy.[18]

IR causes serious DNA damages, such as a double-strand break-DSB or just a single-strand break (SSB). On DNA-DSB breakage, an IR-induced lesion develops whenever the complementary strands of the DNA double helix are simultaneously injured, in close proximity. In addition, this breakdown may induce inappropriate recombination (non-homologous junctions), thus giving rise to chromosomal mutations.[19] Since ATM patients are susceptible to IR, radiotherapy is generally discouraged for these patients, and there is a need for a careful evaluation of the cost and benefit of this therapeutic approach, thus reinforcing the need to diagnose individuals with ATM mutations, in order to avoid their exposure improving their quality of life and prognosis.[20]

Final Considerations
The inclusion of ATM research in the tumor markers used in the clinical routine may allow better treatment adaptation protocol for patients with ATM. For patients with a family history of early breast cancer (≤50 years) but without clinical manifestation, the diagnosis of TMJ may help in taking preventive measures. In patients already diagnosed with breast cancer, the choice of target therapy and the determination of the genetic profile may be a preponderant factor for the longer survival, especially if performed before defining the treatment protocol, especially radiotherapy. In this context, the genetic profile research may help in choosing a targeted therapy, contributing to a lower risk of recurrence and increasing the survival of the patient with breast cancer.

INTEREST CONFLICTS

There is no interest conflicts between authors.

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