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Mutated Ataxia-Telangiectasia and Its Correlation with the Incidence of Neoplasms: A Literature Review

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Abstract: *Ataxia-telangiectasia (A-T) is an autosomal recessive condition that manifests itself in childhood and is characterized by progressive cerebellar ataxia, Purkinge cell degeneration, stagno-ponderal delay, and others neurodegenerative manifestations. Genetically, AT individuals have mutations in the ATM protein (mutated telangiectasia ataxia), which is directly associated with the cellular mechanism of response to DNA damage. ATM can exert its function by acting on key proteins of the cell cycle that are induced in response to a variety of stimuli, including oxidative stress, hypoxia, growth factor stimulation, through the phosphorylation of their targets, with consequent modulation of activity and of the function of these proteins. Due of the role of ATM in stopping the cell cycle, deficient cells of this protein fail to induce verification of genetic damage, resulting in DNA replication and error propagation, until this damage becomes too severe for the genome and the cell is targeted for alternative suicide route, independent of p53. Cells of any functional ATM protein are hypersensitive to radiation, and do not normally respond to any DNA damage. Instead of activating cell repair, cells without ATM, when subjected to radiation, induce the accumulation of mutations in other genes, leading to cell growth, followed by uncontrolled division. This uncontrolled growth can induce the formation of malignant tumors. Research has shown its alteration in cancer patients, with mutations being more common in lymphoid tumors and tumors related to breast/ovarian syndrome. Knowing the influence of ATM on the predisposition to the development of hereditary neoplasias, this review aims to gather the main findings regarding this mutation, and to relate them to the neoplasias associated with it and already described in the literature.*

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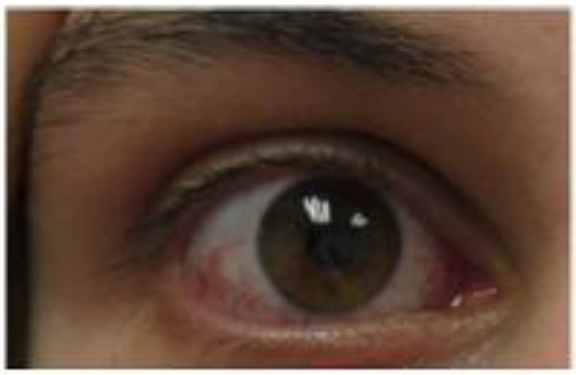
I. Introduction

Ataxia-telangiectasia (A-T) is a rare, hereditary, multisystemic disorder that affects the nervous system, the immune system and predisposes individuals to develop cancer. It occurs between 1 in 40.00 and 1 in 300.000 births, and the first symptoms appear even in early childhood, when children begin to walk[1]. This syndrome is characterized by progressive cerebellar ataxia, with degeneration of the Purkinge cells, state-ponderal delay and progressive dementia, oculomotor apraxia, frequent infections, choreoathetosis, conjunctiva's telangiectasia, immunodeficiency, tendency to respiratory system infections, sensitivity to ionizing radiation, and an increase in cases of cancer with a higher risk of malignancy[2,3,4,5,6] (Figure 1).

Figure 1: Ocular telangiectasia in person with A-T Source: Cynthia Rothblum-Oviattet al. (2016).



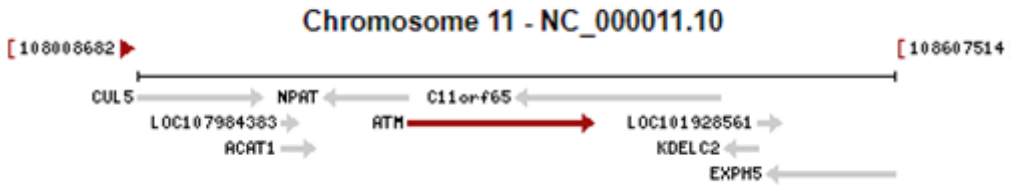
People with A-T have an increased risk of developing autoimmune or chronic inflammatory diseases. This risk is possibly a side effect of immunodeficiency, and the most common examples of A-T disorders include immune thrombocytopenia and various forms of vitiligo[7]. The mechanism that relates to immunodeficiency and A-T is still not well understood, however, it is believed that a dysfunction in a gene called mutated ataxia-telangiectasia (ATM), necessary for the processing of the double strand DNA, which allows for rearrangements V(D)J (somatic recombination), and is responsible for normal maturation of certain types of immune cells (such as T lymphocytes), is responsible for defects in lineages of the cells of the immune system, causing changes in signal transduction for antigen recognition and clonal expansion[13].

Genetically, A-T is an autosomal recessive disorder, and the germinal inactivation of the ATM is responsible for this pathology[8]. A-T individuals have mutations in the ATM protein, associated with the cellular mechanism of response to DNA damage. These individuals have mutations in the two copies of the gene of each ATM cell, presenting an undetectable intracellular level or absence of ATM catalytic activity[9].

The gene was mapped in 1988 by genetic linkage analysis, and identified by positional cloning in 1995[9,10]. This mutation in ATM protein is associated with the cellular mechanism of response to lesions in DNA[11]. The prevalence of mutations in the ATM gene is 0.5-1% in the western population. More than 300 mutations have already been described, of which about 80% are by substitutions, insertions or deletions of bases, causing premature terminations of codons or splicing abnormalities. Only 10% of ATM mutations cause A-T[5].

ATM is a serine/threonine protein belonging to a phosphatidylinositol-3-kinase family (PIKKs). This hereditary gene is located in the long arm (Q) of chromosome 11 between positions 22 and 23 (11q22-23) (Figure 2). More precisely, the ATM gene is located from the base pair 108.222.500 to 108.369.102 bases pairs on chromosome 11, and covers about 150 kilobases of genomic DNA, containing 66 exons. It is expressed in a wide variety of tissues as a 13-kilobase transcript, and encodes a 350-kd protein[5,10,12].

Figure 2: ATM gene location on the human chromosome. Source: NCBI (2017).



II. Materials and Methods

This study constitutes a descriptive narrative review on the most relevant aspects about the ATM gene and the influence of ATM on the predisposition to the development of hereditary neoplasias. Data collection was performed between 2017 and 2018, 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 "AtaxiaTelangiectasia (A-T)", "Ataxia Telangiectasia Mutated", "ATM" and "cancer". The inclusion criteria were scientific articles that explored the proposed theme, published between the years 1987 and 2016. 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.

III. The role of ATM in the cell and repairing DNA damage

Every day, the cells are invariably challenged by tens of thousands of lesions[14]. In order to maintain genomic stability, cells have developed sophisticated signaling pathways, allowing replication damage or stresses to be resolved[15]. If the DNA is not repaired correctly, the lesions from the repair failure may be lethal to the cell, or may even lead to deleterious mutations. As a consequence, cellular inviability occurs, or induction of atypical behaviors, allowing the development of malignant neoplasias. A collective signaling network known as DNA Damage Response (DDR) orchestrates DNA detection and repair, ensuring maintenance, genetic stability and cell viability[16].

The C-terminal kinase domain of the ATM is flanked by two regions called FAT (FRAP, ATM and TRRAP) and FATC (FAT C-terminal), which participate in the regulation of its kinase activity[17]. ATM kinase plays a central role in mediating DNA damage, either in response to double-strand breaks in the chain, or by inducing cell cycle drag and facilitating repair through its target proteins[15]. Thus, ATM is a central regulatory protein of the DNA damage response, and in the loss of its function, in homozygous individuals, leads to the

development of A-T[18]. In relation to the cell cycle, this gene regulates and interacts with different substrates, including proteins that activate cell division control points in G1, S or G2-M, as shown in Table 1[19].

These genes control complex signaling pathways involved in DNA repair, cell cycle arrest, chromatin remodeling, senescence and apoptosis, responding to DNA damage by phosphorylating the major substrates involved in cell cycle repair and/or control (Figure 3)[6,18,20,21]. ATM, when stimulated by DNA damage, can be activated by different pathways, promoting cell repair, cell cycle drag, chromosome remodeling, and apoptosis. For DNA repair, the complex MRN, BRCA1 (Breast Cancer 1), RAD51 and a tumor suppression protein 53 (p53) are activated; in cell cycle arrest are involved the SMC1 proteins, CIP/KIP family via p53, and checkpoint kinases for chromatin remodeling, Chk1 and apoptosis c-Abl, p53, Chk2, E2F1, p73 and NFkB[18].

In response to DNA damage, the ATM is activated by its dissociation of dimer to two partially active monomers, and these monomers are then directed to the lesions sites[17,22]. Numerous autophosphorylation events of ATM to S1981 are essential for the dissociation process[17,22,23]. As mentioned previously, the recruitment of ATM for DNA repair is dependent on a number of complexes. Among them are the complexes MRN, RAD50 and NBS1. The activation of ATM is also dependent on the mediator of damage control MDC1, which is recruited to the lesion site along with the interaction of histone gamma 2AX (□-H2AX)[24]. Upon activation, ATM sends signals to downstream targets (toward the 3' of the DNA molecule) in order to initiate an optimal DDR. The elements involved in ATM detachment, when the optimal response is completed, include a wild type p53-induced phosphatase 1 (WIP1), and a phosphatase protein type 2C[25]. In addition to the protein-protein interaction and the post-translational modification involved in the activation of ATM during DDR, the ATM expression itself can be negatively regulated by microRNA (MiR)-421, MiR-18a and 106a[26,27].

With DNA damage, the entry into the S phase of the cell division will be reduced, causing an accumulation of the cells in the G1 phase, in order to avoid the replication of the damaged DNA. Direct ATM targets on G1/S control point activation include p53, E3 ubiquitin-protein ligase, COP1 (COP1), a control point protein 2 (Chk2), Mdm4 p53 (MDMX) and Rad9[24].

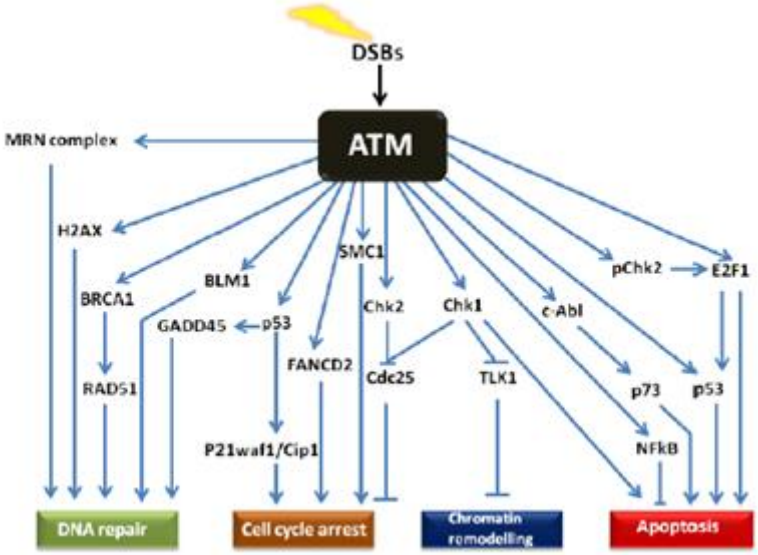
In normal, non-stressed cells, p53 is a short-lived protein, and its degradation is promoted by MDM2 (Mouse Double Minute). After DNA damage, ATM and Chk2 (phosphorylated by p53) reduce p53's ability to bind to MDM2, thus contributing to its stabilization. In addition, ATM can directly phosphorylate MDM2 to S395, which leads to a reduction in its activity. MDM2 is stabilized by DAXX (deathdomain-associated protein), a multifunctional protein located in the nucleus and cytoplasm of the cell, which controls the regulation of apoptosis events. Phosphorylation-dependent ATM weakens the MDM2-DAXX interaction, facilitating p53 activation. Together, these mechanisms lead to the stabilization and nuclear accumulation of p53, which, in turn, promotes the transcriptional activation of the p21 CDK inhibitor. P21 inhibits CDK2-cyclin activity leading to cell cycle arrest in the G1/S transition[17,28].

Thus, ATM acts on innumerable targets within the cell, through control of growth rate and cell division, played central role in the normal development of cells and in the activity of various physiological systems. The ATM protein coordinates DNA repair by activating enzymes that recognize and fix damaged or broken ribbons, which have been altered by agents such as radiation or chemicals substances. Interruptions of DNA strands can also occur naturally when chromosomes exchange genetic material during cell division. If DNA repair is efficient, it will help maintain the stability of the genetic information by the cell, otherwise it will multiply erroneously and propagate the genetic damage[20,29].

Table 1: ATM substrates at different stages of the cell cycle. Source: Khalil et al. (2012).

G1	G1/S	S	G2/M
p53 Mdm2 Nbs1	p53 c-Ab1 Rad51	RPA Chk2 FANCD2 H2AX BRCA1 CtIP MRN	Chk1 Chk2 Rad17 (RFC)

Figure 3: ATM signaling pathways. Source: Khalil et al. (2017).



IV. Correlation between Atm and Neoplasias Incidence

The pathogenesis of cancer can be attributed to mutations in the DNA that have an impact on cell growth and migration. Tumor-related mutations may include single-base substitutions, insertions, deletions, and aberrations in the number of copies. Mutations of a single nucleotide, which comprise, in particular, those of sense exchanged and meaningless, are more common. Recently, efforts have been made to distinguish missense (mismatched) mutations associated with tumors of common polymorphisms, which exert their effect on the primary amino acid and functional protein sequences. In contrast, other mutations, called nonsense, result in truncations, exchange of protein or non-functional products, which are generally unstable and result in the expression of absent or severely reduced protein with impairment in its functioning[30].

Cells lacking any functional ATM protein are hypersensitive to radiation and do not functionally respond to DNA damage. Instead of activating the repair, the nonfunctional ATM protein induces the accumulation of mutations in other genes, causing the cells to grow and divide in an uncontrolled fashion. This uncontrolled cell growth may induce the formation of malignant tumors[5,6,31].

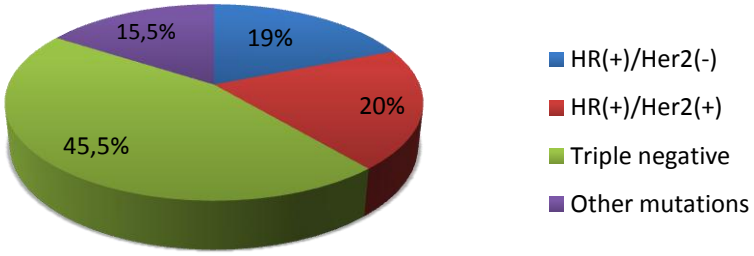
It has been more than 40 years since the first time the hypothesis arose that ATM heterozygous individuals could have an increased risk of developing neoplasms. Subsequent studies characterized the genetic variant of this protein, and described its functions in response to DNA damage[32]. The predisposition to lymphomagenesis is a well-known phenomenon of A-T. Inactivation of ATM has been described in sporadic malignant lymphoid neoplasms, supporting the role of ATM as a tumor suppressor gene. However, it is still unclear whether heterozygous individuals for mutant ATM are at higher risk of developing tumors. However, the case of an ATM heterozygote patient who developed a mantle cell lymphoma (LCM) following occupational exposure to ionizing radiation and somatic mutation of the second ATM allele, has been described in the literature, supporting the claim that heterozygous ATM changes in combination with exposure to irradiation predispose to sporadic LCM[33].Currently, heterozygous individuals for ATM gene mutation are estimated to be twice as likely to develop breast cancer compared to the general population. This risk is raised five-fold in women younger than 50 years, and the gene's penetrance is approximately 15%, predicting that these mutation carriers will develop breast tumor is not accurate[34].

Several studies have attempted to assess the potential of the most common ATM gene variants in breast cancer (BC) susceptibility. Three large case-control studies did not find any evidence of association for variants with a less frequent allele of greater than 5%. Other studies evaluated associations for the coding of variants with intermediate frequency (1-5%), but the results are inconsistent, which concludes that more combined association studies are needed to clarify this issue[35].

A study of 133 patients with an early diagnosis or family history of BC revealed, according to the molecular subtype of breast tumor, the prevalence of the ATM gene mutation in 19% patients with hormone receptor positive (HR), Her2 negative, 20, 0% in patients with HR positive, Her2 positive, 0% in patients only in Her2 positive, and 45.5% with triple negative breast cancer ($p = 0.024$) (Graph 1). Seven of nine of the BRCA1 mutations and the single FANCI mutation were in the triple negative group; nine of 11 mutations in BRCA2 (Breast Cancer 2), 1 of 2 in RAD50, as well as mutations in BRIP1, MSH2, MUTYH and RAD51C were in the

cases of hormone receptor positive and Her2 negative, and mutations in RAD50, ATM and TP53 were in the HR positive, Her2 positive group[36].

Graph 1: Prevalence of dysfunctional MV versus hormone receptors.



In vitro and *in vivo* studies investigated the role of ATM in modulating HER2-dependent tumorigenicity, where it was possible to demonstrate for the first time evidence that ATM also acts as a tumor promoter gene. ATM was able to promote tumorigenicity in HER2-positive BC cell lines. This relationship wasdemonstrated due to the role of ATM interaction between HER2 and the Heat Shock Protein 90 (HSP90), the main stability modulator of the HER2 protein. Inhibition of ATM significantly reduces HER2-HSP90 complex formation, resulting in HER2 ubiquitination and degradation. Thus, identification of the role of ATM in HER2-positive tumor expression provides evidence for the dual role of ATM in the development of neoplasms[37].

Parameters of genetic susceptibility may play a minor role in most cases of neoplasias, usually 5-10% of all cases. In less than 5% of cases, genetics play a more significant role, causing the hereditary syndrome known as the "breast/ovarian cancer" syndrome. This includes those individuals who carry the BRCA gene mutation. These mutations represent up to 90% of the total genetic influence with a BC risk of 60-80% in affected individuals. Other significant mutations include p53 (Li-Fraumeni Syndrome), PTEN (Cowden's Syndrome), STK11 (Peutz-Jeghers Syndrome), CHEK2, BRIP1 and PALB2, in addition to ATM[38].

Many genetic mutations have been detected in epidemiological studies; however, in Brazil, the first study to investigate the occurrence of mutations in the ATM gene in BC patients presented a 7% index with alterations in this gene, most of them missense type variations. The exact prevalence of ATM mutations, mainly of the nonsense type, which leads to the formation of the "truncated protein", with erroneous protein transcription still not known[39].

V. Diagnostic methods and therapeutic conduct

ATM protein can be detected by *Western Blot* (WB) in cases where the level of kinase activity is still present. Individuals who have mutations in the ATM gene but still have the mutation detected by WB are traditionally referred to as "atypical" or "variant", and more recently have been classified as "mild". When there is some degree of residual in ATM function, both normal and mutant, the overall severity of clinical course is lower, and disease progression is slower[7].

The immunohistochemical technique (IHC) can be applied diagnostic in the diagnosis routine with complementary to the cancer for the identification of diagnostic and prognostic biological markers[40]. Immunocytochemistry (ICQ) is currently the most used method of analysis for the detection of cell cycle regulatory proteins, but it is a time-consuming and labor-intensive technique[41]. In addition, molecular biology methods such as New Generation sequencing - NGS have been used in the construction of genetic panels[42].

In the last decade, the cloning of several genes that predispose the development of cancer has facilitated the emergence of predictive tests, based on molecular analyzes of DNA, allowing access to patients and relatives to this type of molecular diagnosis[43].

About 5% of all BC have a hereditary component related to mutations in autosomal dominant genes. Currently, few known genes cause BC. The predisposition to this type of cancer associated with the ATM gene is known, and due to the estimated frequency of heterozygous individuals in the general population. Its nonfunctional activity may be related to this percentage of individuals who develop CM. On the other hand, it has been observed that the 1100delIC mutation of the CHEK2 gene acts as an allele of susceptibility to CM of low penetrance[44].

Since BRCA mutations account for only 10 to 20% of BC cases in patients with early onset or family history of cancer, and since New Generation Sequencing (NGS) technology allows the simultaneous sequencing

of a large number of target genes, genes predisposing to the development of cancer are beginning to be considered in the diagnosis of neoplasias, but their meaning in clinical practice is not yet consensus among the medical class[36].

The NGS technique promotes DNA sequencing on platforms capable of generating information on millions of base pairs in a single run. This technique is extremely important in the detection of genetic alterations of various types. Research has demonstrated the importance of the NGS technique, since it provides a genetic panel of 34 genes associated with solid tumors. Through the detection of translocations it is possible to identify congenital malformations, recurrent spontaneous abortions, infertility and propensity to tumor development[45].

Multiple gene sequencing studies verified the sensitivity and specificity of the NGS platform against results obtained by PCR in the identification of genetic variants, among them the ATM gene. The results were fully consistent with the results obtained in amplification by the PCR technique[36].More recently, several signatures of gene expression have been developed as tools for classification, prognosis and treatment adaptation at the onset of breast cancer. Among the first and best validated assays are the Polymerase Chain Reaction (PCR) based on the result of 21 genes (commercially available as Oncotype DX)[45, 46]. This technique is useful in clinical practice to predict sensitivity to chemotherapy in patients with ER positive breast cancer, negative lymph node, and to avoid exposure to chemotherapy toxicity for patients with low recurrence score.MammaPrint evaluates the expression of 70 genes related to the initial risk of metastasis, including invasiveness and angiogenesis, as well as measuring reference genes (normalization genes and negative control genes) in triplicate[45,46].

Therefore, these technologies allow, in addition to detecting the altered gene accurately, to locate and identify which mutation is related to the clinical outcome[45]. Target gene capture in the NGS assay provides an average reading depth of about 1000-fold, which facilitates the simultaneous detection of single nucleotide variants and variants of the exonic copy number in a comprehensive evaluation. Exons with insufficient coverage (<20 times depth of reading) or high sequence homology (pseudogenes) are complemented by amplification fragment-based sequencing with specific primers to ensure a percentage coverage of all target regions[47].

Breast cancer is the most common malignant disease in women, with an almost triple increase from an annual incidence of 600,000 in 1980 to 1.6 million in 2010. It is also the second leading cause of cancer-related death in the world and incidence rates are increasing especially in developing countries.ATM dysfunctional individuals present increased sensitivity to ionizing radiation. X-ray exposure should be limited when it is required for diagnostic purposes. Radiation therapy for cancer or any other reason is usually detrimental for individuals with A-T and should be performed only in rare circumstances and in reduced doses[7].

Genetic counseling is recommended for patients with breast cancer precursor or relevant family history. This strategy significantly reduces cancer-related mortality in carriers of the genetic mutation, who receive regular screening or prophylactic mastectomy and oophorectomy. Other non-BRCA pathogenic mutations may explain breast tumors in patients with early onset or significant family history. Of the non-BRCA genes reported as being of medium to high penetrance in hereditary breast carcinoma, are the ATM, BRIP1, PALB2, PTEN and CHEK2[36]. From a clinical point of view, patients with mutated ATM should have limitations and peculiarities in cancer treatment, such as avoiding radiotherapy due to radiosensitivity, and it is prudent to diagnose and warn AT heterozygotes about their possible risk of malignancies and to offer them a prevention for neoplasias, since they occur more frequently in relatives of patients with mutated ATM, as well as the follow-up and prevention of relapses. It is especially important to start this program early, as therelative risk of death by ATM is greater for heterozygotes before 45 years[48].

VI. Conclusion

ATM activation modulates all cellular machinery that determines the fate of the cell through its repair components. The presence of dysfunctional ATM in both homozygous and heterozygous individuals is a key point for failures in the various control and repair centers of DNA molecules. Its change leads to non-phosphorylation of target proteins involved in the cell division cycle as well as failure in repairs to the damage generated on the double strand. Individuals with this mutation will be deficient in lymphocyte cell synthesis, susceptibility to ionizing radiation and predisposing to the development of hereditary neoplasms. It is of the utmost importance that this gene be detected through molecular screening and diagnostic tests, since radiotherapy represents a trigger for the dysfunctional activation of the ATM. Therefore, its early detection allows to assist in the therapeutic management of patients diagnosed with neoplasias, mainly lymphatic or breast/ovarian cancers, helping to reduce the mortality and morbidity and mortality of these individuals, providing an increase in life expectancy, decrease in relapse cases and quality of life to these patients.

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