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ATM Mutations and Radio-sensitivity: A Review of Molecular Pathology and Cancer Susceptibility

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Abstract
Hereditary mutations of genes involved in DNA repair have resulted in increased susceptibility to a variety of cancers. Mutations in ataxia telangiectasia mutated (*ATM*) gene result in an autossomal recessive disorder ataxia telangiectasia syndrome (AT), which manifests with greater predisposition to various types of cancer, radiotherapy resistance and adverse prognosis. Therefore, patients with AT and their cells are radiosensitive, mainly because ATM protein kinase is a regulator of DNA damage identification and cell cycle control in response to ionizing radiation. Blood relatives of AT can also carry a pathogenic *ATM* mutation, which presents similar or even other risks (not yet completely described), although apparently healthy. Due to the unusual phenotype of radiosensitive cells in ATM patients, it has been the focus of numerous studies in the past two decades. The efficiency of radiotherapy treatment among ATM patients has been questioned due to its toxic effect on normal tissue. As certain ATM signaling provided valuable information about the response to DNA damage and cancer, but the understanding of the role of ATM in radio sensitivity is still incipient and, therefore, the molecular determinants of the clinical response are poorly understood so far. On the face of these considerations, this work presents a review of the normal structure and function of the ATM with compilation of the current literature on the risk of radio sensitivity and malignancy among patients with mutations in the ATM.

Keywords
Ataxia Telangiectasia Mutated, *ATM,* DNA damage, DNA repair, radiation therapy, cell cycle checkpoint, cancer.

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I. INTRODUCTION
Activation of checkpoint arrest and DNA repair are necessary to maintain genomic integrity during DNA replication. Defective DNA repair is seen in cancer and results in genomic instability and the accumulation of other genetic abnormalities (1, 2). Thus, cancers with mutations in the genes that encode proteins involved in DNA repair may be more sensitive to treatments, inducing DNA damage or inhibiting complementary DNA repair mechanisms (3).

Hereditary mutations of genes involved in DNA repair, such as ataxia telangiectasia mutated (*ATM*), are causative of ataxia-telangiectasia syndrome (AT), a rare autosomal recessive systemic disorder first described more than 60 years ago(4), which result in

considerably increased susceptibility to a variety of malignancies, ranging from 10% to 20% (5, 6). Cancer types risk includes lymphoid, gastric, breast, central nervous system, skin, and others. In adition, progressive cerebellar ataxia, immunological defects, insulin-resistant diabetes and radiosensitivity can occur in this patient characterized by biallelic mutations in the *ATM* gene. Besides that, a large number of mutations (more than 600) can occur in the ATM coding and noncoding regions (7), and the patient's response varies depending on the type of mutation. ATM protein kinase is involved in many cellular functions, including response to DNA damage, control of the cell cycle checkpoint, apoptosis (8) oxidative stress and mitochondrial metabolism (9). It integrates the cellular response to damage by phosphorylation of the main proteins involved in cell cycle regulation and DNA repair and, therefore, lack of normal ATM function in inherited AT syndrome results in a pleiotropic clinical syndrome characterized not only by a marked increase in the risk of cancer but also profound hypersensitivity to ionizing radiation. Cells derived from patients with AT presents genomic instability, loss of normal cell cycle arrest pathways, defects in DNA repair and increased sensitivity to radiation. These mechanisms indicate the ATM play an important role in maintaining genomic integrity and, therefore, in the mechanism of cancers pathogenesis (10, 11).

ATM is a gene known to be associated with radiosensitivity in the germ line, studies show that its inhibition increases the sensitivity of cancer cells to radiotherapy, one of the most frequently used treatments for different types of cancer, in order to eliminate the cells tumors, but the molecular determinants andclinical response in ATM patients are still poorly understood (12). In this sense, this narrative review aims to provide an overview in order to outline the current understanding of the predictive potential of *ATM* gene mutation to respond to the risk of radiationtoxicity and radiation therapy, as well as the susceptibility to cancer among patients with AT mutations.

II. RESULTS AND DISCUSSION

Structure and functions of ATM

The *ATM* gene was first identified in 1995 through studies of AT syndrome (13). It locates in the human chromosome 11q22-23, includes 66 exons with a 9168-base pair. ATM is a powerful protein kinase, member of the phosphatidyl inositol 3 (PI3K) like protein kinase (PIKK) family, that encodes a human PI3K serine/threonine PIKK that helps maintain genomic integrity (14). This protein is involved in a multitude of cellular processes. It has been well described that it plays an important role in the normal development and activity of body systems, including the nervous and imunesystems. It also attends to cells in recognizing damaged or broken DNA strands. In this context, it plays a central role in the repair of DNA double-strand breaks (DSB), which can be induced by several mechanisms, including: ionizing radiation, chemotherapy drugs, or oxidative stress, or even occur during normal physiologic events like meiotic recombination or rearrangement of antibody genes during B-cell maturation (15, 16).

It is a consensus within the scientific community that ATM has extensive roles in DNA damage response signaling, and plays a critical role in the signal transduction of cell cycle checkpoint, the repair of damaged DNA and the apoptosis(14). Some authors report that ATM is a master regulator of DNA damage response (17).

The ATM protein location is predominantly nuclear in most cell types (where it exists as a non-covalent homodimer) and also in subcellular organelles. This form of protein is catalytically inactive in the resting state cells, but with DNA damage it is rapidly activated and converts to an active monomer from that phosphorilates a large number of substrates involved in a diverse array of cellular process, like cell cycle checkpoints and DNA repair(18). Thus, ATM responds locally to specific DNA damage, phosphorilating the main substrates involved in DNA repair and/or the cell cycle control (14).

Once activated (when DNA damage is detected), ATM phosphorylates a large number of downstream effectors, which then phosphorylate its own targets. It has been described that there are more than 700 targets after DSBs and also that *ATM* modulates networks that are not immediately involved in DNA repair, such as the insulin-like growth factor or other metabolic and stress-response pathways (19).The abundance of ATM targets are probably a means of coordinating several pathways in the event of DNA repair or genomic stress (20).

Considerable progress has been achieved in delineating the role of ATM in controlling the cell cycle checkpoint, given the large number of researches in this field. However, the focus of current research is the relationship between ATM and signaling pathways in certain events, such as type of tumors and sensitivity to radiation/radiation treatment in these events, as well as personalized pharmacological treatments in AT patients. The central question here seems to be what the best

therapeutic approach is to be indicated for these patients.

III. The role of ATM in damage response induced by radiation

Cell cycle checkpoints are crucial and can improve cell expansion and limit mutagenic events after DNA damage. It is already known that ATM mediated signaling pathways (Figure 1) play an essential role in the responses of the checkpoint of the radiation-induced cell cycle, such as that induced by ionizing radiation (21).

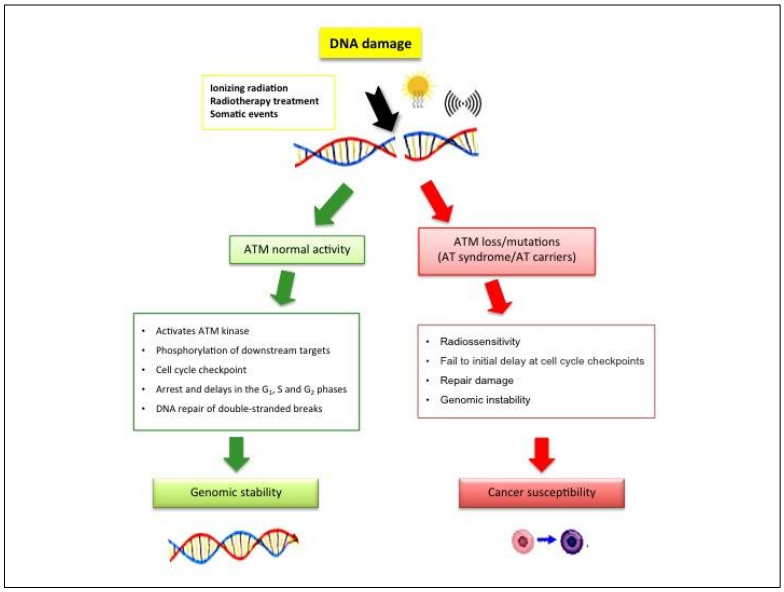

Figure 1: Model to explain the role of ATM in DNA damage response. ATM maintains the DNA integrity and, consequently, genomic stability, activating multiple cellular functions. A defect in the ATM leads to abnormal responses to DNA damage and consequently to cancer susceptibility.

In response to radiation-induced DNA-damage, ATM kinases are activated quickly, which in turn triggers phosphorylation of their respective downstream targets, including p53, kinesin-associated kap-1 protein (KAP-1), as well as the checkpoint kinases 1 (CHK1) and 2 (CHK2) (13, 22), two serine/threonine protein kinases (Ser/Thr), that play an important role in the regulation of the cell cycle and in the phosphorylation of p53, which plays an important role in the control of the cell cycle and in apoptosis.

The activation of CHK1 and CHK2 results in phosphorylation of Cdc25, leading to sequestration, degradation and / or subcellular inhibition (inhibitory phosforilation) that normally activates Cdc2 / cyclin B at the G2 / M limit (23). CHK2 can also phosphorylate p53-Ser20 to bring stabilization of the p53 protein after radiation. The activation of p53 by ATM, ATR and CHK2 kinases leads to the induction of p21 protein, which can directly inhibit the activity of the Cdc2 / Cyclin B complex, which governs entry into mitosis (22). Additional evidence supports a direct role of ATM in other checkpoints of the cell cycle, which includes c-Abl, a protein tyrosine kinase, and beta-adaptin, an endosomal protein, among others (24).

This activation lead to cell cycle checkpoints, arrests and delays in the G1, S, and G2 phases of the cell cycle and even allows DNA repair of double-strand breaks, both by homologous recombination and by non-homologous final union (15, 16). The G1/S interface ATM has been shown to play a central role in radiation-induced activation of the p53 tumour suppressor gene product, since ATM binds to p53 in a complex way and activates the molecule in response to breaks in DNA. The signaling pathways of the radiation-induced cell cycle checkpoint promote cell cycle arrest, which, in turn, contributes positively to cell survival in response to this event (8, 25). Therefore, ATM levels are not altered after exposure to ionizing radiation, but ATM kinase activity increases after exposure several times (21).

Cells of patients with AT syndrome fail to show initial delay at several checkpoints of the cell cycle after irradiation. In addition, a defect in the induction of p53 by ionizing radiation was evident in these patients. In this sense, the ATM gene mutation leads to the functional and structural alteration of the ATM protein in the these patients, leading to the occurrence of abnormalities in the cell cycle checkpoint and DNA damage repair, leading to an increase in sensitivity to apoptosis. The *ATM* gene

mutated production the human genetic disorder AT is a 350 kDa protein that plays a central role in the regulation of several cellular processes. Therefore, defects are observed at all cell cycle checkpoints in post-irradiation AT cells (26, 27).

It is likely that environmental radiation exposure may have a greater effect on certain ATM genotypes / variants and may induce different modifications in cellular responses in these patients. In this case, the importance of radiation exposure as a risk factor must be examined in epidemiological analyses stratified by genotype (28).

ATM and Radiosensititity

ATM is described as one of the main regulators of the cellular response to radiation-induced DNA damage and a key determinant of radiosensitivity (28). This evidence has been demonstrated by several previous studies that have shown a leading role for ATM kinase in the regulation of cancer cell radioresistance (29, 32)

On the other side, radiation therapy is an approach to cancer treatment that has unquestionably significantly improved the local control of the disease and the overall survival of cancer patient. In general, radiation hinders the growth of cancer cells by inducing cytotoxicity, caused mainly by DNA damage (29).

DNA damage induced by ionizing radiation can significantly affect whether a cell will proliferate, differentiate, become senescent, or go into apoptosis (30, 31). In general cellular properties (such as cell type and tissue of origin) determined the DNA damage associated cell-fate decisions (32). Even the physiological properties of the cells, including the ability to detect, repair, and tolerate DNA damage, are likely to be important determinants of fate when cells are exposed to to varying degrees of DNA damage (33).

In addition, the amount and quality of DNA damage also affects these decisions about the fate of cells. Thus, the dose rate of sparingly ionizing radiation is particularly important, since lower dose rates produce smaller biological effects, even when the total dose is kept constant (34).Hickson and cols (24) confirm these data and suggest that inhibition of ATM should radiosensitize tumors. They showed that fibroblasts and tumor cells are radiosensitized to X-ray radiatiotherapy (XRT) in culture by pharmacological ATM inhibition, or by ATM mutation and deletions (35). However, caution is needed when using this strategy clinically, due to the possibility that normal tissues may also be sensitized as well. This reluctance is well founded, as it is based on the previous dire response of patients with AT to XRT already described.

Thus, cells harboring loss-of function ATM deficiencies demonstrate extreme radio sensitivity. Further, AT syndrome is often referred to as a genome instability or DNA damage response syndrome. For this reason, the efficiency of radiotherapy has been considered very limited in patients with biallelic mutations or deletions of ATM due to its toxic effect on normal tissue (36).

Cao and cols (33) have been demonstrated a critical role for the ATM tumor protein p53 (TP53)/p21 pathway in the regulation of DNA-damage-associated cell fate. Cultured mouse cells were exposed to various amounts and qualities of ^{137}Cs γ-irradiation and then and then the effects of this irradiation on different types of human cells were monitored. The researchers showed that inhibition of ATM/TP53/p21 complex change the responses to DNA damage, leading to micronucleus formation in chronically irradiated cells, the measure of which assesses genomic instability. In addition, the study clearly demonstrated that the ATM/TP53/p21 pathway regulates the relationship between DNA-damage tolerance and response when cells were exposed to chronic γ-irradiation and that this decision depended on the dose rate and the cell type. The TP53 pathway was a critical component of cellular responses to chronic γ-irradiation, which were triggered by the rate of DNA damage.

A recently published study evaluated whether radiation therapy affects contralateral breast cancer risk in women with ATM pathogenic germline variants (among others) in breast cancer. This study described that rare ATM missense variants, currently not identified as pathogenic, were associated with risk of radiotherapy(37).

It is very important to identify the critical determinants of radioresistance and to develop safe and effective tumor radiosensitizers, especially considering patients with ATM gene deficiencies. Thus, taking these processes into account, there is still an extensive field of research for the development of ATM inhibitors (ATMi) as anticancer agents (38).

ATM mutations and malignancy risk

The ATM gene is mutated in the autosomal recessive disorder, AT syndrome, characterized by an increased risk of susceptibility to cancer throughout life (39, 40), and may be related to the radiosensitivity, resulting in chromosomal and chromatid breaks.

The types tumors are diverse in patients with AT. Previous data indicate a high incidence of lymphoid neoplasms, most notably T-cell acute lymphoblastic leukemias. Recently, B-cell non-Hodgkin´s lymphoma and Hodgkin´s lymphoma was also reported to be more frequent than initially recognized. Patients with AT also develop carcinoma, but less frequently and at an older age than lymphoid cancers (40-42).

Another category, AT mutation carriers, are generally healthy individuals who have a mutated copy of the *ATM* gene, such as the parents or other blood relatives of a person with AT syndrome. However, a systematic meta-analysis found that patients with *ATM* mutation have a short lifespan due to cancer (breast and gastrointestinal tract) and ischemic heart disease (43).

More than 400 disease-related mutations have been described in ATM gene, which may be due to mutations in a homozygous or compound heterozygous germline. ATM mutations identified in AT families can be divided in three categories; truncating mutations, mutations that lead to some expression of mutant protein that does not have kinase activity and missense mutations with reduced kinase activity(44). Approximately 70% of the disease-related mutations result in the production of truncated protein (45).

ATM carriers who are heterozygous for ATM gene variants are often asymptomatic and largely considered healthy carriers. Despite this, it has been described that they are more sensitive to ionizing radiation and susceptible to ischemic heart disease, diabetes, and cancer, specially breast cancer, and that of digestive tract, lung and lymphoid origin (46, 47).

Monoallelic ATM mutation carriers are also at risk of malignancy, particularly breast cancers, and many association studies have been conducted on breast cancer susceptibility. Initially, epidemiological studies on relatives of AT patients revealed a two to five-fold increase in the risk of breast cancer for female obligate ATM carriers (20, 48, 49).

ATM mutations are associated with an increase of approximately two to to three times the risk of breast cancer, however, for patients with a familial history of the disease, risk estimates increase even more,which is probably due to other risk increasing variants in the families (50, 51).The increased risk of breast cancer in patients with ATM was confirmed by direct *ATM* sequencing in breast cancer cases compared to controls(49). *ATM* is also considered a moderate-penetrance cancer susceptibility gene in *BRCA1/2*-negative patients with familial early-onset breast cancer (52).

Another recently published study (53) evaluated deleterious germline mutations in ATM by PCR-Sanger sequencing 7657 in BRCA1/2 negative breast cancer patients and founded 31 pathogenic mutations in the ATM gene across 30 carriers. The ATM mutation rate was 0.4% (30/7.657). Those patients were significantly more likely to have family history of breast and/or ovarian cancer (26.7% in carriers vs. 8.6% in non carriers). Another study corroborates these data when using the multigenic panel by next generation sequencing method to identify that *ATM* was mutant in non-*BRCA1/2* patients with hereditary risk of breast cancer (54).

Next-generation sequencing has led to the recent discovery that pathogenic ATM variants are often identified in patients with pancreatic ductal adenocarcinoma with and without a family history of the disease. In addition, it was described that the loss of ATM was also a frequent somatic event in the development of these type of cancer (55). ATM was recently described using a complete exome sequencing technique as one of the most frequently mutated germline genes in aggressive prostate cancer (56). Another molecular method was used to evaluate the relation between ATM polymorphism and gastric cancer in the Chinese population. The study found that the ATM polymorphism was related to increased susceptibility and worse prognosis (57).

Along with mutations associated with AT , several ATM examinations in cancer patients have identified missense ATM variants, particularly amino acid substitutions that are not expected to be associated with AT (58). However, discrimination of these ATM variants from ATM polymorphisms and their contribution to health risks is still controversial (59).

A national cohort study carried out in the registry of the French National Reference Center for Primary Immune Deficiencies (CEREDIH), conducted by Suarez and cols (40) evaluated retrospectively the incidence of cancer in 279 patients with AT syndrome. The follow-up of patients with AT with malignant neoplasms was 13.9 years and the incidence of malignancy was 24.7% among them (1,571 events per 100,000 person-years) and did not vary across decades. The median age at diagnosis of malignancy of any type was 12.5 years and differed significantly across the groups of tumors (an average age of onset of Hodgkin´s lymphoma is 10.6 years old and carcinomas, 31 years old). Lymphoid neoplasms, particularly acute lymphoblastic leukemia, Hodgkin´s lymphoma, and non-Hodgkin´s lymphoma, represented the majority of cancers. The study (40) showed that the cumulative incidence of cancer was 10.4% at 10 years, 22.6% at 20 years, 29.9% at 30 years, and 38.2% at 40 years. By age 10 years, 1.9%

of patients had developed lymphoblastic leukemia, 2.3% Hodgkin´s lymphoma, and 6.2% non-Hodgkin´s lymphoma. At 20 years of age, 3.5% of patients developed acute lymphoblastic leukemia, 5.5% Hodgkin´s lymphoma, and 13.6% non-Hodgkin´s lymphoma. No patient developed acute lymphoblastic leukemia or Hodgkin´s lymphoma after age 20 years. At age 30, 17.6% of patients developed non-Hodgkin´s lymphoma, 2.6% T-PLL and 0.8% a solid tumor. At 40 years of age, 20% of patients developed non-Hodgkin´s lymphoma and 6.6% a solid tumor (40). This study also showed that solid cancers (such as breast, gastric, liver, and thyroid) comprised mostly carcinomas.

The patient's family and personal history is important for identifying and diagnosing tumors. In a retrospective study of 279 patients with AT syndrome, 69 had cancer and most were hematological cancers, including the majority as 38 cases of non-Hodgkin's lymphoma (60)

Although the precise mechanisms of malignancy in AT are not fully understood, it is considered to be primarily related to the role of ATM in maintaining genomic stability. However, the exact contributions of the various ATM functions, the immunodeficiency associated with AT and possible extrinsic factors remain unclear until now. Immunodeficiency associated with AT is variable, and its causal relationship with the development of cancer is questioned(17, 38).

III. CONCLUSION

Considering the unusual radiosensitive phenotype of cells from AT patients, ATM has been the focus of intense scrutiny for the past two decades. In order to improve the efficacy of radiation therapy in AT carriers, it is necessary a better understanding of the signaling network that drives ATM mutated cell to be cancerous and then to overcome radiation-induced cytotoxicity.

The treatment of ATM mutations in cancer patients is challenging, because the impact of antineoplastic treatment on response and toxicity is not well established. Survival after cancer is considered short in TA patients, but long-term remissions are possible. The risk of second neoplasms is still not well established in these patients, and there is no consensus in the scientific community. Recognition of clinical and biological heterogeneity in the ATM mutation, both for AT syndrome and for AT carriers, is thought to be at least in part associated with the type of ATM mutations, and patients with loss of function mutations appear to have different susceptibility cancer and different survival rates.

The identification of patients with a mutable or pathogenic ATM variant of the germ line and, therefore, a greater susceptibility to the development of some types of cancer, is essential for the early detection that is advocated in improving patient care, detecting cancer before metastases, contributing to the improvement of the patient's prognosis and life expectancy.

Despite the great efforts of the scientific community, we can conclude that there is a great gap with regard to the therapeutic conduct of ATM patients. Well-designed studies are still needed to contribute to a better understanding of cancer susceptibility in AT patients, and its relationship with radio sensitization, in addition to ATM-mediated signaling, to cause cells to stop the cycle and start DNA repair The analysis of these genotypes can eventually be applied clinically to determine treatment modalities in affected patients.. Taken together, targeting ATM in association with another genetic panel can be a promising strategy for cancer treatment.

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