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A Narrative Review of ATM Diagnosis Methods: Comparative Analyzing

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Abstract: *Germline mutations are the underlying cause of AT syndrome which predisposes to a wide spectrum of early-onset cancers, particularly of lymphoid origin. Besides that, some studies have been pointed out that AT mutation carriers, generally healthy, can have a reduced lifespan due to cancer, specially breast and gastrointestinal tract and also ischemic heart disease. Because AT syndrome is so rare, the symptoms or criteria for making a diagnosis are not familiar in the medical field. A diagnosis of AT can usually be made by the combination of clinical features and specific laboratory abnormalities, mesasured by a wide range of methods.*

Here, we summarize the current knowledge on ATM variations detection methods, as flow cytometry, immunohistochemistry (IHC), whestern blotting and real-time polymerase chain reaction (RT-PCR). Also, we delineate the recent literature about ATM as a cancer biomarker and a potential target for anti-cancer therapies.

Keywords: *Ataxia-Telangiectasia Mutated; Heterozygozys, Laboratory Measurement, Detection Methods, Protein Activity.*

1. INTRODUCTION

The *ataxia-telangiectasia mutated (ATM)* gene was first reported in 1995 as the causative gene responsible for Ataxia Telangiectasia Syndrome (AT) (1) *ATM* gene is located on chromosome 11q22-23(2) which encodes a protein of the same name (3) which is a phosphoinositidyl 3-kinase (PI3K)-family kinase (4). Is a mediator of DNA damage response which induce cell cycle arrest and DNA repair via their downstream targets. ATM has also an essential role in the DNA double-strand break (DSB), wich is formed when DNA is damaged. For this reason, AT is often referred to as a genome instability syndrome, DNA damage response syndrome or a cromossomal instability syndrome (3).

Most AT patients do not have functional ATM protein due to missense or non-sense mutations in the *ATM* gene, which result in truncated or unstable ATM variants (5). For this reason, AT is a complex disease, and not every people have the same clinical presentation, symptom constellations and/or laboratory findings. So far, different forms or presentations of AT have been described in the literature, with those more severe variably categorized as “classic”, “typical”, “early onset” or “childhood onset” AT, while milder forms have been referred to as “variant”, “atypical”, “late onset” or “adult onset” AT (2).

The diagnosis of AT is usually suspected due to the combination of neurologic clinical characteristics (ataxia, abnormal eye movement control, and postural instability) with one or more of the features which may vary in appearance: telangiectasia, frequent sinopulmonary infections and specific laboratory abnormalities (e.g. IgA deficiency, lymphopenia especially affecting T lymphocytes and increased levels of alpha-fetoprotein). As certain neurological features can arise later, a diagnosis of AT should be carefully considered for any ataxic child with an otherwise elusive diagnosis. A diagnosis of AT can be confirmed by the finding of an absence or deficiency of the ATM protein or its kinase activity in cultured cell lines, and/or identification of the pathological mutations in the *ATM* gene (2).

Not only AT patients, but also certain *ATM* heterozygous mutation carriers have a reduced life expectancy and cancer specific types susceptibility, thus, certain *ATM* heterozygous mutation carriers should be made aware of lifestyle factors that contribute to the development of such diseases (6).

Considering that downregulation of *ATM* has been described at mRNA and protein levels, this narrative review aims to outline the *ATM* gene and investigated techniques to quantify ATMs as part of laboratory protocol methods.

2. Analyzing *ATM* DNA Damage Response by Flow Cytometry

Flow-and image-assisted cytometric approaches is used to assess the mechanisms and measure the extent of DNA damage response in individual cells, as cell cycle phase position, levels of reactive oxygen species (ROS) and induction of apoptosis. This method requires a few tissue and can count thousands of cells in a few minutes, and multiple antibodies can be used simultaneously on a single tissue sample (7).

Under non-stress conditions ATM forms dimers or oligomers. DNA damage induces intermolecular autophosphorylation of serine 1981 that causes dimer dissociation to monomeric units that initiates intracellular ATM kinase activity (8). So, activation of ATM occurs through its autophosphorylation on Ser1981. Besides that, other autophosphorylation sites as Ser367, Ser1893, and Ser2996 are physiologically important parts of the DNA damage response (9). Also, ATM phosphorylates many proteins involved in control of cell cycle checkpoint, apoptosis, and DNA repair, including p53, Chk2, BRCA1, RPAp34, H2AX, SMC1, FANCD2, Rad17, Artemis, and Nbs1(10).

Examples of cytometric detection of activation of ATM protein kinase using phospho-specific Abs targeting Ser1981 of this protein, are already described. Activation of ATM protein kinase by its phosphorylation on Ser1981 and phosphorylation of histone H2AX on serine 139 (γH2AX) are the key events reporting DNA damage, primarily formation of DNA DSBs (11).

DSBs are formed when DNA is damaged, whether it is endogenous or exogenous, it is always followed by the phosphorylation of the histone, H2AX, the first step in recruiting and localizing DNA repair proteins. Is phosphorylated by ATM and ATM-Rad3-related (ATR) in the PI3K pathway. All these events are detected immunocytochemically in individual cells using phospho-specific Abs. Flow-and imaging-cytometry, the latter exemplified as laser scanning cytometry, is used to quantify intensity of cellular fluorescence reporting activation of ATM and induction of γH2AX with respect to cellular DNA content, which in turn reports the cell cycle phase (12)

In one study published by Li and cols, flow cytometry was used to examine the percentage of cell apoptosis and G2 phase arrest in glioma stem cells. The authors hypothesized that both high expression of *ATM* and glioma stem cells are responsible for radioresistance in glioma and concluded that silencing of ATM via the siRNA technique improved radiosensitivity of glioma stem cells both in vitro and in vivo (13).

Besides that, the cytometric assay of DNA damage has been used to test the role of ROS as the agents mediating DNA damage. This is seen in one study those suggests that aside from increased tumorigenesis, ATM-deficiency results in altered metabolism, aberrant immune and inflammatory responses and increased levels of ROS. In addition, ATM can be directly activated by ROS, independently from DSB signaling, and has been implicated in mitochondrial quality control, potentially through an ability to localize to mitochondria (14) In this study, data was analyzed using flow citometry and mean fluorescence intensity was used as a measure of ROS (15).

Cytometric assessment of ATM activation provides a very sensitive and convenient tool to estimate DNA damage. Some authors may expect, therefore, that multiparameter cytometry will be the methodology of choice in analysis of reporters of DNA damage such as ATM activation (11).

3. ATM as a Cancer Biomarker

CpG islands hipermetilation studies: epigenetic changes in ATM

Epigenetic characteristics in white blood cells (WBC) are promising risk markers candidates for solid tumors (16). DNA methylation, an epigenetic change, can be a biologic indicator of lifetime accumulation of environmental exposures including ageing, hormones, ionizing radiation, alcohol, smoking, and traffic particles. Dysregulation of epigenetic modification in tumor DNA such as hypermethylation of CpG islands at the promoters are focused on the most studies on DNA methylation. However, more recently regions around CpG islands or “shores” and intragenic sequences also appears to be important in tissue-specific expression and may be an important contributor to interindividual variation in gene expression (17).

The presence of methylated CpG islands in the promoter region of genes including *ATM* can suppress their expression. Some studyes suggest that hypermethylation of *ATM* gene was associated with increased breast cancer risk (16-18). Flanagan and colleagues performed methylation microarray analysis of peripheral blood DNA from 14 women with bilateral breast cancer and demonstrated that was an increased methylation associated with lower ATM mRNA level (16).

The study recently published by Brennan and cols evaluated leukocytes DNA methylation levels at ATM and suggested that it could be a marker of breast cancer risk (18). The evaluation DNA methylation in leukocytes as a biomarker of cancer risk is of particular importance once peripheral blood is often available in prospective cohorts and easier to obtain than tumor or normal tissues samples. It is possible extracted DNA samples from whole blood in the usually CpG sites and used as the measure of methylation (16).

More recently, Cao and colleagues(19) also studied A*TM* promoter methylation in pheripheral blood in breast cancer patients and healthy controls. This study, on the other hand, found no significant differences presented in DNA methylation levels of *ATM* between the sporadic breast cancer cases and the healthy controls. So far, the evidence for powerful blood-based methylation markers is still limited and the identified markers need to be further validated.

Methylation of the ATM promoter is a common event in many types of cancer including breast and colorectal, and may correlate with superior radiosensitivity (20).

These data demonstrates the potential for gene-body epigenetic misregulation of ATM and other cancer-related genes in peripheral blood DNA that may be useful as a novel marker to estimate cancer risk, breast and others.

In the area of molecular epidemiology, where large numbers, control groups, and robust statistics are mandatory, such studies are facilitated by technical advances allowing the identification of DNA mutations extracted from many biological samples such as plasma, urine, sputum, or exfoliated cells from bronchus, bladder, oral cavity, and esophagus. Besides of that, recent study suggests that High Performance Liquid Chromatography (HPLC) method could be a powerful tool for DNA methylation diagnostics, including prognostication of patients with cancers (21). These data shows us the variability of techniques and samples that can be evaluated, whose applicability depends on the objectives to be pursued.

4. *ATM* Genetic Measurement

Mutations and deletions may also serve as biomarkers for diagnosys and targeted therapy

Historically, testing for pathogenic *ATM* variants/mutations has been limited. However, with the current popularization of gene panel assays, more data about the prevalence of those variants among women with a suspected hereditary predisposition for breast cancer have become available. More than 300 different *ATM* variants have been identified thus far, and hence, the clinical significance of any individual variant can be challenging to assess (22). Next-generation sequencing of patient tumors was used to identify the variants in the *ATM* and has revealed that this gene is altered in many human cancers including colorectal, lung, prostate, and breast. Accumulating evidence suggest that at least some ATM variants are associated with an increased risk of breast cancer (23).

The use of multigene panels for the assessment of cancer susceptibility is expanding rapidly in clinical practice, besides this use for stratification of cancer risk be a topic of great controversy in the fields of genetics and medical oncology. Commercially available gene panels for breast cancer risk, as an example, are increasingly used to test for *ATM* and others, as *CHEK2*, *TP53*, *PALB2*, and several other pathogenic gene variants in women in whom a hereditary predisposition to breast cancer is suspected; however, the clinical implications of some of those variants are unknown (24, 25). Testing for moderate-penetrance mutations began in earnest, however, once ‘next generation’ sequencing technologies made it feasible to screen for mutations in many genes simultaneously using multigene panels (25).

Germline variants in *ATM* are frequent events in Chronic Lynphocytic Leukemia (CLL), a highly heritable cancer, with a 7.5-fold increased risk in first-degree relatives. In this case, *ATM* behaving as a classic tumor suppressor gene, showing preferential somatic loss of the wild-type allele (26, 27). Aproximatelly 70–80% of cases exhibit recurrent chromosomal abnormalities that can be identified by fluorescence *in situ* hybridization (FISH). The most common genomic aberration, include deletion in

the q arm of chromosome 11, the site of the *ATM* gene at (11q22.3). Regarding that, aproximately 30–40% of such cases have been reported to have a mutation in the remaining *ATM* allele, currently determined by next-generation sequencing.

After *ATM* gene mutate, DNA damaged could not be accurately repaired and finally accelerates cancer transformation and proliferation. So, mutations in *ATM* are linked to poor prognosis and are commonly, but not exclusively, associated with a chromosome 11q23 deletion. Assays of *ATM* function are currently done by deletion analysis by FISH and *ATM* mutation analysis (28).

Having this in mind, one study evaluated mutations in the *ATM* gene determined by next-generation sequencing and revealed 12 somatic mutations and 15 germline mutations in peripheral blood samples from patients with CLL. But, no strong correlation was observed between *ATM* mutation and function. The authors suggest that a direct assay of the kinase activity should be used an indicator of *ATM* function in the development of therapies, not the mutation status (28).

Germline *ATM* sequence variants have been reported in breast cancer cases, however, it is difficult to fully evaluate the increased risk associated with their presence (29).

RNA expression profiles are increasingly used to diagnose and classify disease, based on expression patterns of as many as several thousand RNAs. Is a method for rapid quantitative assessment of hundreds of transcripts is being implemented in hospital laboratories for diagnosis, prognosis, monitoring, and predicting efficacy of therapy *ATM*-related downstream gene expression profiling may be an useful biomarker for AT carrier detection. Real Time Quantitative RT-PCR and Microarrays are examples of the techniques that measured RNAs. The last, permit measurement of hundreds or even tens of thousands of RNAs simultaneously, including coding and noncoding RNAs (30).

One good example is the measurement of RNA expression in AT carriers. In those patients, one mutant *ATM* allele are usually not severely affected although they carry an increased risk of developing cancer (31).

RT-PCR assays were used to evaluated *ATM* gene expression levels in tumor and adjacent normal tissue from patients diagnosed with primary breast cancer. In this study, *ATM* gene expression was down-regulated in those samples and a high *ATM* gene expression level was associated with a favorable prognosis (32).

A sistematic review published by van Os NJ (33) described that *ATM* mutation carriers have a reduced life expectancy because of mortality from cancer and ischemic heart diseases and an increased risk of developing cancer in particular breast and cancers of the digestive tract. Because of this, the authors propose that all female carriers of 40-50 years of age and female ATM c.7271T>G mutation carriers from 25 years of age onwards be offered intensified surveillance programs for breast cancer. Furthermore, all carriers should be made aware of lifestyle factors that contribute to the development of cardiovascular diseases and diabetes.

5. Structural and Functional Impact of *ATM* Mutations

Protein expression analysis methods: Imunohistochemistry and Western blotting

Immunohistochemistry (IHC) is a method to identify specific antigens within tissue sections utilizing an antigen-specific antibody and also allows morphologic evaluation by light microscope. Detection at the light microscopic level of antigen–antibody interactions can be achieved by labeling the antibody with a substance that can be visualized, either by conjugation to a fluorescent marker or enzyme followed by colorimetric detection. The advantages of IHC include the preservation of all cells in the tissue and the ability to store the paraffin-embedded tissue for long periods, allowing for reuse with additional antibodies (7).

ATM protein underexpression has been described as an independent prognostic factor to breast cancer (34). In this sense, Feng and cols (35) used immunohistochemistry and automated semi-quantitative digital analysis to detect and quantify ATM and Ki67 in resected primary tumors from patients with early stage hormone receptor-positive breast cancer. The authors indicated that the combination of high ATM and low Ki67 is prognostic of improved survival, independent of tumor size, grade, and lymph node status, and suggest that the prognostic value of Ki67 can be improved by analyzing ATM expression in this type of tumor.

One study recentlly published analyzed ovarian cancer tissues and ajacent normal tissues by imunohistochemistry and found that ATM expression was increased in tumor tissues compared to adjacent normal tissues. In this study western blotting was also performed which found the same result for ATM protein expression as detected by immunohistochemistry (36). Besides that, recently Jha and cols (37) investigated the expression of nuclear ATM on 69 formalin fixed paraffin embedded choroidal melanoma samples by immunohistochemistry and validated the results by western blotting method. Loss of ATM was observed in 65% of cases, suggesting this result as a poor prognostic marker in the pathogenesis of uveal melanoma which may lead to increased risk of metastasis.

Using western blotting, it was demonstrated that radiation induced the expression of ATM and p53 protein,

Immunocytochemistry (ICC) is almost the same procedure as IHC, as the steps are the same after fixation of the samples. The difference between two techniques is that ICC examines cell preparations (exfoliated cells, cultured cells and others) while IHC examines tissue sections.

6. Concluding Remarks

ATM deficiency, either in the germ-line or due to epigenetic mechanisms is well known to increase cancer risk and promote breast cancers. Studies on *ATM* mutations/deletions, ATM variants and kinase activity will further contribute to the understanding of gene-environment interactions in cancer, in particular when comparing variations in *ATM* mutation patterns in relation to different cohorts of patients. In summary, this review provided an overview of the methods for measuring the *ATM* gene and activity, described in the literature so far.

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