Review

The ATM Gene and Ataxia Telangiectasia

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Abstract. *Ataxia telangiectasia (AT) is a rare neurodegenerative, autosomal recessive disorder characterized by chromosome instability, radiosensitivity, immunodeficiency and a predisposition for cancer. Epidemiological studies have shown that AT heterozygotes have a predisposition for cancer, especially for breast cancer in women. The disease is caused by mutations in the ATM gene, leading to total loss of the ATM protein, which normally recognizes DNA damage, activates the DNA repair machinery and the cell cycle check points in order to minimize the risk of genetic damage. This review summarizes the clinical features of AT and the natural history of the disease and puts recent molecular advances into the context of the cellular and clinical phenotype.*

Ataxia telangiectasia (AT) is a rare neurodegenerative disorder characterized by extreme sensitivity to radiation and predisposition to cancer (1). Affected children are normal at birth, but by the age of 2 to 3 lose muscle coordination and by the age of 10 are usually confined to a wheelchair (2). Telangiectasia, that is chronic dilation of capillaries leading to the development of dark red blotches on the skin or the eyes, appears after the onset of ataxia. Eye movements are jerky and oculomotor apraxia is common. In addition, patients display cerebral degeneration, sterility and immune system defects. The immunodeficiency phenotype in AT is variable and usually manifests as decreased or absent IgA, IgE and IgG2 (1, 3).

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In young children, the neurological symptoms are often incomplete and the diagnosis of AT is usually possible by the age of 10, when magnetic resonance imaging (MRI) shows significant thinning of the molecular layer of the cerebellum and cerebellar atrophy (4). Although substantial advances have been made in the clinical diagnosis of this disease, treatment for the progressive neurodegeneration is lacking and only symptomatic therapy of secondary symptoms is offered to the patients. The cause of death is often pneumonia, or chronic lung disease resulting from immunodeficiency, or from defects in chewing and swallowing due to the progressive neurological impairment (2, 4, 5).

AT is transmitted as an autosomal recessive disorder, has an incidence of about 1 in 40,000-100,000 births and seems to have an ethnic component (6-8). The carrier frequency is estimated to be approximately 1%. It is important to distinguish AT from other autosomal recessive cerebellar ataxias, such as Friedreich ataxia, oculomotor apraxias 1 and 2, Aicardi syndrome and Nijmegen breakage syndrome (6).

Laboratory Investigation of AT Patients

Elevated levels of serum α-fetoprotein (AFP) are detected in more than 95% of AT patients. This finding is used for the diagnosis of AT and in order to distinguish it from AT variants (2). It is not clear why AFP remains high in AT patients, since there is no obvious liver damage and it is thought that it may be due to abnormal regulation of RNA transcription in the absence of ATM protein (ATM) (5). Cytogenetic investigation reveals chromosome instability, accelerated telomere shortening, radiosensitivity and sensitivity to other DNA damaging agents. In addition, chromosome analysis of peripheral blood lymphocyte cultures reveals an increased incidence of translocations involving mainly the loci of immunoglobulin and T-cell

receptor genes on chromosomes 7 and 14. These translocations can be detected in 10% of circulating T-cells in AT patients during their lifetime (5).

Molecular Basis of AT

The gene responsible for AT, ATM, is localized on chromosome 11q23 and was cloned in 1995 (9). Molecular analysis has indicated that the disease is due to mutations in the gene, which spans more than 150 kb, is composed of 66 exons (62 coding) and encodes a 350 kDa protein kinase. ATM protein is fairly large, almost exclusively nuclear, and is expressed in most of the tissues (10, 11). Over 400 distinct AT mutations have been described and most of the patients are compound heterozygotes inheriting distinct AT mutations from each parent (12). About 85% are null mutations, resulting in premature protein truncation, causing complete inactivation of the gene and absence of a protein product. Less that 15% are missense mutations or short in-frame deletions or insertions (5, 13-16). Mutations are reported in every part of the gene with no hot spots (3).

ATM protein contains a phosphatidyl-inositol 3-kinase like enzyme that is involved in cell cycle control, mitotic recombination, telomere length monitoring and DNA damage response (17). A rapid increase in kinase activity occurs after exposure to ionizing radiation or in the presence of double-stranded breaks (18). The phenotypic manifestation of AT is due to the broad range of substrates for the ATM kinase, involving DNA repair, apoptosis, various checkpoints in the cell cycle, gene regulation, translation, initiation and telomere maintenance (6, 19).

ATM and p53 are two proteins that are believed to play a major role in maintaining the integrity of the genome. They both cooperate in enforcing G_1 and G_2 checkpoint control and ATM-dependent phosphorylation is directly responsible for p53 activation (1, 11, 20). Alterations in these proteins may contribute to an increased incidence of genomic changes, such as deletions, translocations and amplifications, which are common during oncogenesis. Initial evidence came from reports of AT patients who had fatal reactions to radiation therapy. In addition, cell lines derived from AT patients exhibit defects in several ionizing radiation-induced cell cycle checkpoints, the most critical of which is arrest in the G_2 phase (18).

The primary function of ATM, therefore, is to respond to DNA damage, in particular to double strand breaks (14, 21) (Figure 1). A crucial survival function when double- strand breaks occur is the inhibition of the cell cycle through the activation of cell cycle checkpoints (15).

Checkpoints occur to introduce a pause in proliferation, in order to address cellular stress. For this reason, it is believed that proteins that influence checkpoints are required to prevent cancer, and factors involved in DNA damage response are often linked to the activation of checkpoints. Since many ATM substrates are key effectors of the cell cycle, cells derived from AT individuals have defective cell cycle checkpoints after DNA damage due to defective phosphorylation of ATM substrates (11).

ATM and Telomere Length Maintenance

Telomeres, found at the ends of eukaryotic chromosomes, prevent their erosion, facilitate the recruitment of telomere-binding factors and stop the activation of the DNA damage response pathways. In humans, progressive telomere shortening causes impaired proliferation and premature senescence of cells. During senescence, ATM goes to shortened telomeres and prevents cell cycle reentry (22). Since the development of lymphocytes goes through periods of rapid proliferation, telomere erosion and cell cycle dysfunction may generate the immunodeficiency noted in AT patients. In humans, ATM deficiency results in accelerated telomere loss and T lymphocytes derived from AT patients exhibit frequent telomeric fusions (23). Although the telomere erosion observed in AT patients is thought to underlie their accelerated aging, there is no evidence of a correlation between telomeric fusions and risk for leukemia or lymphoma (23).

ATM and Cancer

Since cancer is linked to genomic instability, individuals who suffer from syndromes characterized by defects in DNA damage responses are usually cancer prone (Figure 1). Approximately one third of AT patients develop cancer, mainly leukemias and lymphomas which develop in childhood and are a common cause of death (6, 11, 27). Of these cases, 40% are non-Hodgkin's lymphomas, 25% leukemias and 10% Hodgkin lymphomas. Most leukemias and lymphomas are of T-cell origin (10). Solid tumors in AT patients are usually adenocarcinoma of the stomach, dysgerminoma, gonadoblastoma and medulloblastoma (24). The range and frequency of tumors are thought to be due to genome instability arising from defective recognition and repair of double strand DNA breaks, as well as defective cell cycle check points. Typical cytogenetic changes seen in tumors from AT individuals often involve rearrangements at the T-cell receptor loci (1). In lymphoid malignancies, missense mutations of the AT gene, rather than truncating mutations are usually identified (24).

Epidemiological studies have consistently shown that female relatives of AT patients, carriers of the mutation, have an increased risk for developing neoplasia, particularly breast cancer, suggesting a dominant expression of the defective gene, even though the disease is an autosomal recessive disorder. Combined analysis of the available data
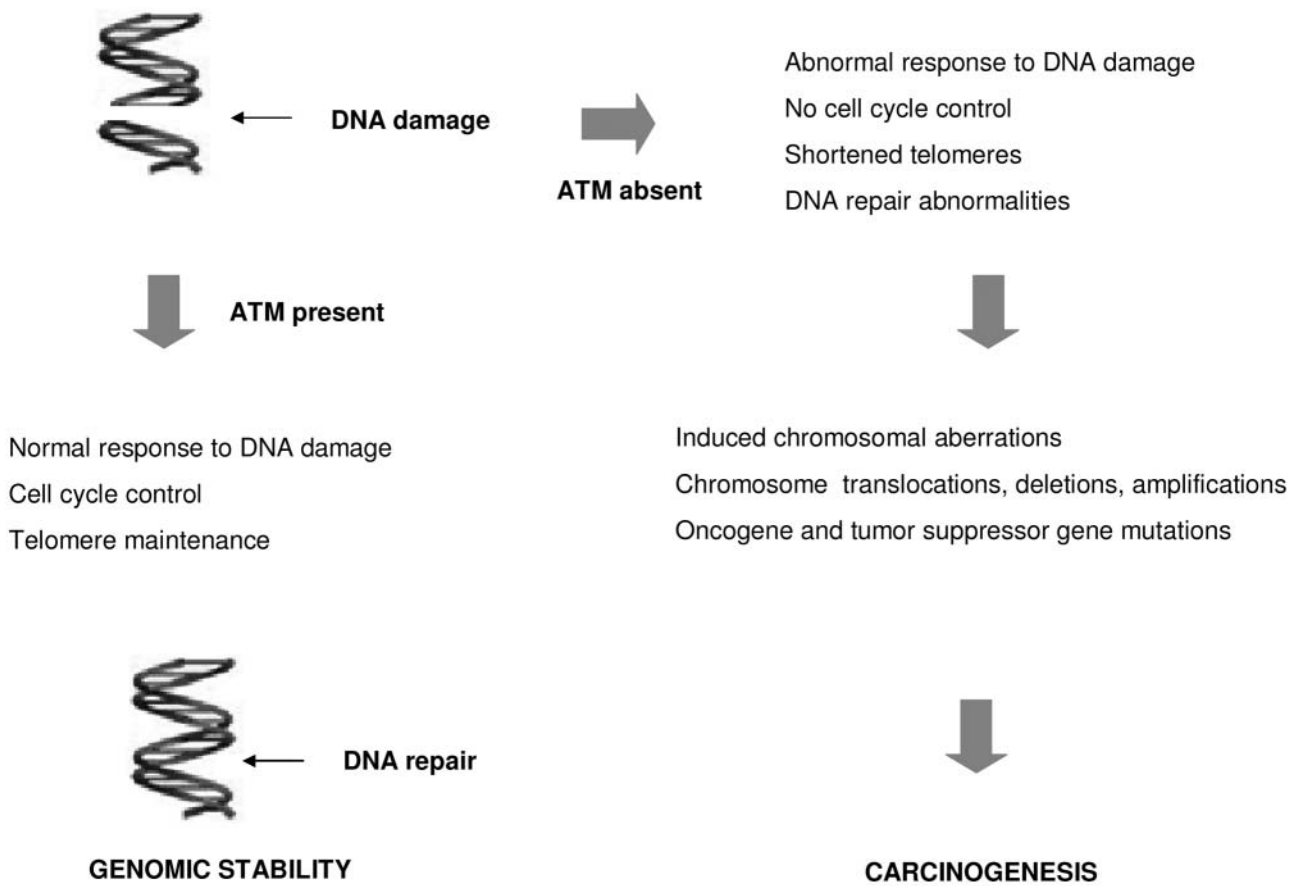
Figure 1. *Contribution of ATM protein to genomic stability and cancer susceptibility.*

has led to an estimate of 3.9% for the increased breast cancer risk in women (25).

Genetic predisposition accounts for 5-10% of hereditary breast cancer and BRCA1 and BRCA2 are two genes known to be responsible for only a small proportion of cancer susceptibility. It seems, therefore, that other more common and less penetrant gene mutations may play a role in the remainder of genetically predisposed breast carcinomas (26). One gene which meets these criteria and clearly plays an important role in breast tumorigenesis is ATM (27). The status and expression of the ATM gene in breast carcinomas has been examined using a variety of approaches. Loss of heterozygosity in the region of the ATM gene on chromosome 11q22-23 has been reported in up to 40% of sporadic breast tumors in the lowest grade tumors and at the earliest stages of breast cancer (12). In these cases, ATM protein expression is reduced in the tumors, as compared to the protein levels found in the normal tissues and it seems that this loss of expression is an early event in breast tumorigenesis (12).

ATM and Neurodegeneration

The most prominent symptom of AT is neurodegeneration. By approximately the age of four years, deterioration of gross and fine motor skills occurs, as well as oculomotor apraxia and rapid involuntary movements of the hands and feet. Progressive cerebellar ataxia follows (6). Although substantial evidence supports a causal role in responding to DNA damage, there is no clear picture, as yet, of ATM function in the nervous system (27). Several syndromes associated with DNA repair deficiencies also show neurological defects, indicating that proper DNA damage responses are necessary for homeostasis of the nervous system. Genetic insight into the requirement for DNA repair during the development of the nervous system was obtained from mice in which DNA ligase IV was deleted (26). It is known that ligase IV deficiency activates ATM to initiate neural apoptosis. One function, therefore, of ATM in the nervous system is to eliminate neural cells that cause DNA damage and failure to do this may lead to the accumulation of genetic lesions which can influence cell viability (28).

AT Related Disorders

As well as for AT, defective DNA damage responses underlie the molecular basis of other neurodegenerative syndromes that are closely related to AT. Molecular cloning has now allowed for the distinction between AT and other autosomal recessive cerebellar ataxias such as Friedreich ataxias 1and 2, Aicardi syndrome, AT-like disorder (ATLD) and Nijmegen breakage syndrome (NBS). It is now clear that patients with AT variant syndromes have mutations in genes other than AT (1). Mutations in the MRE11 gene, for example, lead to the development of ATLD, a less severe form of AT (29, 30), and in NBS1 gene to Nijmegen syndrome, phenotypically similar to AT but with distinct neurological defects (30). It is believed that all AT-related conditions are characterized by extreme radiosensitivity and must be caused by deficiencies at common genetic pathways like AT (7).

Conclusion

Genetic instability and abnormalities of the nervous, immune and reproductive systems are among the complex clinical features of AT. In addition, patients display a predisposition to lymphoid malignancies and extreme radiosensitivity. The cause for radiosensitivity remains controversial and is generally attributed to checkpoint defects, abnormal apoptosis and DNA repair abnormalities. ATM protein is believed to have a role in controlling recombination repair but the underlying defect is unclear. Although AT is a rare neurodegenerative disease, understanding its biology will lead to a greater understanding of the fundamental processes that are involved in cancer and neurodegeneration.

Acknowledgements

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