The neurological phenotype of ataxia-telangiectasia: Solving a persistent puzzle

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**Abstract**

Human genomic instability syndromes affect the nervous system to different degrees of severity, attesting to the vulnerability of the CNS to perturbations of genomic integrity and the DNA damage response (DDR). Ataxia-telangiectasia (A-T) is a typical genomic instability syndrome whose major characteristic is progressive neuronal degeneration but is also associated with immunodeficiency, cancer predisposition and acute sensitivity to ionizing radiation and radiomimetic chemicals. A-T is caused by loss or inactivation of the ATM protein kinase, which mobilizes the complex, multi-branched cellular response to double strand breaks in the DNA by phosphorylating numerous DDR players. The link between ATM’s function in the DDR and the neuronal demise in A-T has been questioned in the past. However, recent studies of the ATM-mediated DDR in neurons suggest that the neurological phenotype in A-T is indeed caused by deficiency in this function, similar to other features of the disease. Still, major issues concerning this phenotype remain open, including the presumed differences between the DDR in post-mitotic neurons and proliferating cells, the nature of the damage that accumulates in the DNA of ATM-deficient neurons under normal life conditions, the mode of death of ATM-deficient neurons, and the lack of a major neuronal phenotype in the mouse model of A-T. A-T remains a prototype disease for the study of the DDR’s role in CNS development and maintenance.

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1. Ataxia-telangiectasia: a prototype of genomic instability syndrome

1.1. The disease

Ataxia-telangiectasia (A-T; MIM #208900) is a human autosomal recessive disorder with a complex and variable phenotype that affects several body systems and tissues [1–8]. It is caused by null mutations in the ATM gene [9,10], which encodes the protein kinase ATM, the master regulator of the cellular responses to double strand breaks (DSBs) in the DNA [11–14]. A-T demonstrates the typical consequences of defects in the DNA damage response (DDR): degeneration of specific tissues affecting particularly the nervous and immune systems, chromosomal instability, sensitivity to specific DNA damaging agents, and a cellular phenotype that reflects the missing DDR player. During the last 5 decades A-T has attracted the attention of numerous clinicians and investigators, who recognized the important biological function flagged by its striking phenotype. Recent progress in understanding the ATM-mediated damage response has provided a wealth of information on...
how mammalian cells cope with DNA damage by activating the multi-branched damage response network [12,13,15–18]. Many of A-T’s characteristics can now be safely explained thanks to these insights. However, attempts to explain the cardinal feature of A-T – the neuronal degeneration affecting mainly the cerebellum – have continued to cause unrest among researchers who try to bridge the bench to bedside for A-T patients.

A-T is a multisystem disease but is stereotyped by its neurological symptoms [2,4–7]. These symptoms typically emerge as truncal ataxia, which is usually noticed as the child begins to walk, and subsequently spreads to affect the extremities and then speech. Appearance of involuntary movements (choreoathetosis) follows, and most A-T patients become wheelchair bound by the end of the first decade of life. The underlying pathology is primarily progressive cerebellar cortical degeneration involving mainly the Purkinje and granule cells, although impairment of the extrapyramidal movement system is also common among A-T patients. Degenerative changes in several parts of the CNS are noted later in life, including in dentate and olivary nuclei, spinal cord and ganglia, cerebrum, basal ganglia and brain stem. Overall, the neurological picture is that of marked, relentless progressive neurodegeneration, with the cerebellum most strikingly affected.

Other major characteristics of A-T are telangiectasias (dilated blood vessels) that variably appear in the ocular sclerae and sometimes in the facial skin and ears; primary immunodeficiency affecting the humoral and cellular systems with hypogammaglobulinemia (mainly affecting IgG2, IgA and IgE levels), lymphopenia, and repressed response to a wide range of antigens; predisposition to sinopulmonary infections; striking predisposition to lymphoid malignancies at an early age and epithelial ones at a later age; marked sensitivity to the cytotoxic effect of ionizing radiation (IR); and chromosomal instability evident as elevated breaks and translocations, the latter involving mainly the sites of the immune system genes. Other laboratory hallmarks are elevated serum levels of alpha-fetoprotein and carcinoembryonic antigen [4–6].

In addition to the chromosomal instability, the cellular phenotype demonstrates profound deficiency in responding to DNA damage inflicted by ionizing radiation and radiomimetic chemicals, with the critical DNA lesion being the DSB. ATM-deficient cells exhibit acute sensitivity to DSB-inducing agents, and attenuation of the complex network of responses normally mobilized by this DNA lesion: activation of the cell cycle checkpoints (in proliferating cells) and modulation of numerous metabolic pathways [11–13,16,17,19,20].

1.2. Molecular basis

The cardinal role of the ATM protein in the DDR has been firmly established in numerous studies that employed commonly used, tumor-derived or immortalized cell lines. In these cell lines, ATM is swiftly activated following the induction of DSBs in the DNA and subsequently phosphorylates a plethora of substrates that play key roles in the numerous branches of the DDR [12,13,15,18]. Many of these proteins are phosphorylated on several sites by ATM and ATM-activated protein kinases such as Chk1 and Chk2. These phosphorylations, and often additional post-translational modifications carried out by ATM-activated enzymes, can affect the activity, stability, subcellular location and interactions with other proteins of these ATM targets, thereby modulating the corresponding pathways and processes. In view of ATM’s prime responsibility for activating the DDR in the face of a critical DNA lesion, the question arises why its complete absence leads to a slowly progressing disease with variable phenotype rather than a more severe phenotype. Part of the answer probably lies in the redundancy between ATM and its close relative, the protein kinase ATR. ATM and ATR belong to the PI3-kinase-like protein kinase (PIKK) family, which includes also the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs) and the protein kinases mTOR and hSMG-1 [21]. ATR responds primarily to UV damage and stalled replication forks but is activated also by single strand DNA stretches formed by DSB resection [21–23] and thus cooperates with ATM on phosphorylating several targets in response to DSBs [23–26]. Indeed, the ATM-mediated DDR is not abolished in A-T cells but rather attenuated. The A-T phenotype should be viewed in light of this belated DSB response in the absence of ATM. Another important facet of ATM function is the dependence of its activation and recruitment to the damaged sites of several proteins that belong to the top-tier “sensor layer” of the DSB response. Most notable in this regard are the MRE11-RAD50-NBS1 (MRN) complex [14,27–36] and the MDC1 protein [37,38]. The MRN complex appears to act also upstream of ATR in the DSB response, and this requirement is conserved from yeast to mammalians [39–47].

1.3. Phenotypic heterogeneity and related disorders

The classical A-T phenotype is caused by homozygosity or compound heterozygosity for null ATM alleles, which truncate ATM or completely inactivate it via missense mutations [5,48–50] (see also http://chromium.liacs.nl/LOVD2/home.php). Despite the uniform functional nature of these mutations, there is considerable variability in the age of onset and progression of the symptoms [2,4,5,7,8,48,49,51] (and references therein). Milder forms of A-T, which are characterized by later onset or slower progression of symptoms [48,49,52,53], are associated with leaky splicing mutations or presumed promoter defects that leave residual amounts of functional ATM protein [5,48,49,52–61].

An interesting and important cross-talk between A-T and several related genomic instability syndromes reflects the functional relationships between the proteins mutated in these diseases. A-T-like disease (A-TLD) is similar to mild A-T, having later age of onset and slower progression than classical A-T [62]. A-TLD is caused by hypomorphic mutations in the MRE11 gene [36,63–65]. The MRE11 nuclease is part of the MRN complex [66–68], and the similarity between A-T and A-TLD reflects the requirement of this complex for ATM activation [14,27–35]. Hypomorphic NBS1 mutations underlie the genomic instability disorder Nijmegen breakage syndrome (NBS) [11,69–72]. NBS is characterized by immunodeficiency, genomic instability, radiation sensitivity and predisposition to lymphoid malignancies, but its neurological...
manifestations include microcephaly and mental deficiency. The implications of the phenotypic overlaps and differences between these diseases will be discussed below.

2. Is the neurological phenotype of A-T caused by a DDR defect?

A conceptual difficulty has accompanied the attempts to link ATM function to the neurodegeneration in A-T. ATM has been investigated mainly in cultured proliferating cells, in which an important role of the DNA damage response is to activate the cell cycle checkpoints [11,16,73]. These important pathways were conceived as irrelevant to post-mitotic cells such as neurons. It was further suggested that ATM was cytoplasmic in human and murine neuronal tissues and hence functioning in pathways unrelated to the DNA damage response [74–76].

These intriguing conclusions severed ATM's known function from A-T’s major symptom. Doubts about this notion were raised in our lab when we obtained a molecular explanation for the similarity between A-T and A-TLD: the requirement of MRN for proper ATM activation [27]. One of the conclusions of this study was that the neuronal degeneration in A-TLD, and probably A-T patients, does result from a defect in the ATM-mediated DDR, same as other symptoms of these disorders. We therefore set out to study the subcellular localization of ATM and the ATM-mediated DSB response in neuronal cells. Our studies showed that ATM was largely nuclear and was activated in response to DSBs in human neuron-like cells (NLCs) obtained by neuronal differentiation in vitro [77,78], and in Purkinje and granule cells grown in organotypic cultures derived from mouse cerebellum [79]; we also found that all these cells exhibited vigorous ATM-dependent DDR [77–79]. Nuclear localization of ATM in human cerebellar neurons was recently shown [80]. Although ATM control of some cytoplasmic functions has been shown in the past [81–84] and cannot be ruled out, these results led to the recognition that the neuronal degeneration in A-T is largely caused by the deficiency in the ATM-mediated DDR and focused the attempts to understand A-T on the DDR network in neuronal cells.

3. The ATM-mediated DDR in neurons

The importance of maintaining genomic stability in neurons cannot be over-emphasized and in retrospect should not have been doubted. Their finite number, long life, high metabolic rate, and continuous exposure to oxidative stress on the one hand, and extensive transcriptional activity on the other hand, call for stringent control of their genomic integrity. Nevertheless, it is expected that the DDR of post-mitotic cells will differ in certain respects from that of proliferating cells, e.g., with regard to the cell cycle checkpoints and DNA repair. The neuronal DDR is discussed at length in a number of other contributions in this Volume (Barzilai et al., O’Driscoll and Jeggo, Frappart and McKinnon, and Lavin et al.). Certain aspects relevant to A-T will be emphasized here.

3.1. DSB repair

The repair of the DNA lesion that initiates the DDR is obviously a central arm of this response. DSBs are repaired in eukaryotic cells by the combined action of the nonhomologous end-joining (NHEJ) [85,86] and homologous recombination (HR) [87,88] pathways. The chromosomal breakage and striking sensitivity to IR and radiomimetic chemicals of A-T cells have traditionally been attributed to a DSB repair defect [89]. Attempts to demonstrate this defect have failed for many years because the absence of ATM affects only a small fraction of the breaks, which can barely be detected using conventional biochemical methods [89,90]. A fine difference in DSB repair efficiency between wild-type and A-T cells was demonstrated by Riballo et al. [91], and a similar defect was noted by Pluth et al. [92] in NBS cells. Riballo et al. [91] attributed the DSB repair deficiency in A-T cells to imperfect action of the NHEJ pathway in the absence of ATM-mediated phosphorylation of the Artemis protein. However, Artemis’ activity in the context of DSB repair was later attributed to DNA-PK activation rather than ATM-mediated phosphorylation [93].

DSB repair can be followed by monitoring the disappearance of damage-induced nuclear foci detected by antibodies against the DSB sensors, whose recruitment to the damaged sites marks the presence and location of unrepaired DSBs [37,73,94–97]. Another marker is phosphorylated histone H2AX [98–100]. The difference in the decay of these foci between wild-type and ATM-deficient cells becomes more pronounced when the cells are arrested in G0 [91] (K. Baranes et al., unpublished data), further suggesting that the NHEJ pathway is the main player in the ATM-dependent fraction of DSB repair. Indeed, we found that in human post-mitotic NLCs and mouse CNS tissues, this difference between wild-type and ATM-deficient cells is quite pronounced (S. Biton et al., I. Dar et al., unpublished data). Thus, the subtle but significant reduction in DSB repair capacity in the absence of ATM may characterize neuronal tissues, similar to proliferating cells, and is probably a major contributor to the neuronal demise in A-T. This repair deficiency may reflect a specific type of DSBs, whose repair requires ATM-dependent activation of certain enzymes, or direct action of ATM on repair enzymes that enhances their activity in the face of excessive DNA damage. Detailed examination of possible functional links between ATM and individual components of the DSB repair machineries is thus in place.

3.2. Cell survival vs. programmed cell death

The nature of the critical choice between activation of the survival network or programmed cell death following DNA damage remains unclear [101]. It needs to be reevaluated in view of the recent unveiling of several non-apoptotic programmed cell death pathways that has broken the synonymy between programmed cell death and apoptosis [102]. A pioneering work on the role of ATM in cell death pathways in DNA-damaged neurons was carried out by P. McKinnon and colleagues (see Frappart and McKinnon, this volume), who showed that ATM had a pro-apoptotic function in the developing mouse CNS, in collaboration with the Bax protein [103–106]. They observed that ATM−/− mice exhibited...
resistance to IR-induced apoptosis in diverse regions of the developing CNS, including the cerebellum. ATM-dependent apoptosis occurred in γ-irradiated mouse embryos only in the post-mitotic populations that were present in the neuroepithelial subventricular zone of the developing nervous system. Notably, ATM deficiency did not prevent radiation-induced apoptosis in multipotent precursor cells residing in the proliferating ventricular zone. In wild-type but not ATM−/− mice, up-regulation of p53 coincided with cell death, suggesting that ATM-dependent apoptosis in the CNS was mediated by p53. Furthermore, p53-null animals exhibited similar lack of radiation-induced cell death in the developing nervous system. These studies suggested that ATM may function at a developmental survival checkpoint that serves to eliminate neurons with excessive DNA damage.[103,104,106–108].

This model raises a fundamental question about the neuronal demise in A-T, particularly the gradual relentless loss of neurons in the cerebellar cortex over many years that causes the major neurological symptoms of A-T. Do these cells succumb to accumulated DNA damage that stochastically inactivates critical genes and abrogates important cellular functions, or does the accumulated damage initiate death programs? The second alternative implies that such cell death programs should be ATM-independent (Fig. 1).

3.3. Attempts to re-enter the cell cycle

This interesting and intriguing response of post-mitotic neurons to DNA damage is discussed in detail by Barzilai et al. (this volume). Briefly, following DNA damage, neurons exhibit many parameters characteristic of normal cell cycling but they never show M phase markers and finally undergo programmed cell death.[109–111]. This observation touches upon an important open question in the DDR field—the mechanism behind the cell’s decision whether to survive or to activate programmed cell death in the face of excessive or irreparable damage. This mechanism may be different in proliferating and post-mitotic, differentiated cells. Importantly, Kruman et al. [112] provided evidence for ATM dependence of the cycling attempts of neurons following DSB induction [112]. This observation supports the notion that ATM is involved in initiating programmed cell death in neurons with excessive damage [103–106]. Yang and Herrup [113] noted spontaneous re-expression of cell cycle proteins in ATM-deficient Purkinje cells and striatal neurons from humans and mice at ages at which the cerebellum is still developing. This phenomenon may represent the ongoing stress response in these cells, another facet of the cellular phenotype of A-T [114] (and see below).

The ATM substrates whose phosphorylation we monitored in cultured human NLCs and mouse cerebellar neurons included the checkpoint kinase Chk2 [115] and the cohesin complex subunit Smc1, whose ATM-mediated phosphorylations have been associated with the G1/S and intra-S cell cycle checkpoint [16,73,115–119]. What is the purpose of the phosphorylation of these proteins in neurons? Are they taking part in the apparent attempts of damaged neurons to re-enter the cell cycle following DNA damage? The apparent efforts to re-enter the cell cycle may indeed lead to cell death, but may also serve to create an appropriate physiological environment for the cell’s survival attempts. If the latter, the assumption is that the DNA damage response might be more efficient in a physiological environment that mimics real cell cycle checkpoints (Fig. 1). Further experimentation is required to distinguish between these two suggestions.

4. Recapitulation of the A-T neurological phenotype in the mouse: the failure of the ATM-knockout mouse and the success of the Nbs1–CNS–del model

A major tool in the investigation of a human genetic disorder is the corresponding knockout mouse, which ideally should faithfully represent the human phenotype. The ATM-knockout mouse was initially heralded as “a paradigm of ataxia-telangiectasia” [120]. However, while these mice exhibit many of the characteristics of human A-T, such as retarded growth, immunodeficiency, cancer predisposition, radiosensitivity, infertility and a cellular phenotype similar to that of A-T cells, they barely show the most cardinal feature of A-T, neuronal degeneration and associated neuromotor dysfunction [120–123]. The histopathology of the cerebella of these animals appears normal and the cerebellar phenotype has not been observed even in ATM−/− mice that reached full life expectancy (A. Barzilai, unpublished data). One of these strains, designated ATM(y/y), does show some learning deficits and ectopic, abnormally differentiated Purkinje cells, but no gross cerebellar pathology or overt ataxia [123]. Careful analysis of ATM-deficient mice did
show subtle neurological abnormalities in several instances, including electrophysiological defect, defective response to stimuli that promote neural progenitor cell proliferation, mild motor deficit in stringent behavioral studies, electron microscopic evidence of neuronal degeneration, elevated oxidative stress in cerebellar tissues, and reduced numbers of tyrosine hydroxylase-positive nigrostriatal neurons (but normal levels of monoamine transmitters) [82,123–131]. In vitro survival of ATM−/− Purkinje cells and their dendritic branching were reduced compared to wild-type cells [132,133]. However, these defects were far from the severe human phenotype. Combining ATM deficiency with mutations that increase oxidative stress in double-mutant mice also did not lead to any cerebellar malfunction [134]. This somewhat disappointing phenotype has cast a shadow over the use of these animals for studying the neurological aspects of A-T, and was one of the reasons for the bothersome questions about the very existence of ATM-mediated DDR in neurons. A simple explanation for this difference between mice and humans could be that generation of the A-T cerebellar phenotype in the mouse requires suppression of the DNA damage response system beyond that achieved by eliminating ATM.

Answers to some of these vexing questions were provided by an animal model generated by Wang and co-workers that does exhibit the cerebellar degeneration and ataxia expected by an animal model generated by Wang and co-workers that achieved by eliminating ATM.

Most of the damage inflicted on cellular DNA in body tissues in normal life is probably due not to IR or exogenous radiomimetic chemicals, but rather to normal metabolic by-products. Indeed, oxidative stress resulting from endogenous metabolism is responsible at least in part for the constitutive, low level DNA damage response often detected in cultured cells [139]. Considerable oxidative stress accompanies the intensive metabolic activity in neurons, and deregulated oxidative stress has been consistently associated with various neurodegenerative conditions [140–143] (see also Schmitz et al. and Barzilai et al., this volume). ATM-deficient cells are indeed hypersensitive to oxidative stress-inducing agents such as hydrogen peroxide or t-butyl hydroperoxide (t-BOOH), and radical scavengers (and iron chelators in the case of t-BOOH) can alleviate this sensitivity [144–148]. The clastogenic effect of oxidative stress-inducing agents is enhanced in A-T cells, as is telomere shortening [149]. Furthermore, ATM can be activated by these agents and subsequently mobilize its downstream targets [146,150,151]. It is not surprising, therefore, that neuronal oxidative stress was suggested to contribute to accumulation of DNA damage leading to neurodegeneration in A-T [129,152,153]. Indeed, elevated oxidative stress has been identified in several DNA repair deficiencies including A-T [129,132,154–157]. DDR deficiencies may thus abrogate the delicate regulation of ROS levels and lead to a vicious cycle that further increases oxidative damage to cellular macromolecules, particularly in the CNS [129,130,158–162]. This notion may also explain the constitutive stress response observed in ATM-deficient tissues and cultured cells [114,157,160,161,163–167]. Elevated ROS in ATM−/− mice also affect hematopoietic stem cell function, leading to bone marrow failure—a process that could be corrected by antioxidants [157]. Indeed, antioxidants extended tumor latency in these animals [133,168–171], corrected some fine neurobehavioral deficits [164,171], reduced DNA deletions observed in cultured cells [165], reduced oxidative stress in ATM−/− Purkinje cells and enhanced their survival in culture [132,133], and reduced the constitutive stress response in cultured A-T fibroblasts [114]. Iron chelators enhanced the survival of ATM-deficient cells in culture [167].

An explanation for the increased oxidative stress in ATM-deficient cells was provided by Stern at al. [160], who demonstrated a significant progressive decrease in both the reduced and the oxidized forms of NAD and in the total levels of NADP and NADP⁺ in the cerebella of ATM−/− mice. This perturbation in the balance of pyridine nucleotides may be caused by continuous consumption of NAD⁺ in a major DNA damage-associated response—poly ADP-ribosylation of DNA repair proteins [172]. An alternative explanation is based on inactivation of genes encoding enzymes that control the cellular redox balance following the accumulation of DNA damage [8].
These observations spawned the idea that enhancing oxidative stress in ATM−/− mice might lead to the development of the neurological phenotype that is missing in these animals. Two compound genotypes were established, one combining ATM deficiency with elevated levels of superoxide dismutase 1 (SOD1) [173], and the other ablating SOD1 expression on an ATM−/− background [134]. Both genotypes displayed increased oxidative stress in the animals, but rather than exacerbating neuronal degeneration they enhanced growth retardation and radiosensitivity, two other features of the ATM−/− genotype [134,173]. Presumably the additional amount of DNA damage accumulated in neuronal tissues of these animals did not cross the threshold for inducing neuronal demise that was crossed in the Nbn–CNS–del mouse [135].

Closing the oxidative stress issue, since most of the strand breaks caused in cellular DNA in the CNS still come from ROS, modulation of oxidative stress might offer a therapeutic modality for A-T patients. Several clinical trials based on antioxidants are underway [8].

### 6. Modifiers of the neurological phenotype in A-T

A-T is clearly a monogenic disorder caused by mutations in the ATM gene. However, there is remarkable phenotypic variability among patients who have null ATM alleles [2,8,51]. We recently reported an interesting, somewhat extreme example of this phenotypic heterogeneity in two siblings with exceedingly mild A-T [51]. While this phenotype is usually associated with residual levels of functional ATM and regulatory, missense or leaky splicing ATM mutations [5,48,49,52–61], these patients were homozygous for a null ATM allele. No ATM protein was detected in their cells and their cellular phenotype was indistinguishable from that of patients with the classical picture of the disease. Furthermore, MRI imaging revealed the cerebellar degeneration typical of classical A-T. This family thus represents the action of modifier gene(s) that affect the neurological phenotype of A-T. One modifier of the effect of ATM loss was identified using the mouse model of A-T: the Rad50S allele of the gene encoding the Rad50 component of the MRN complex [174]. This allele partly compensates for the loss of ATM in the mouse, alleviating senescence, radiosensitivity and tumor formation, hallmarks of ATM-deficient mice [175]. This modifier acts in the mouse at the level of the DSB response and is probably hypermorphic for ATM activity [174]. The presumed modifier(s) in the patients described by Alterman et al. [51] exert their effect at the level of central nervous system function. It is pertinent that neurologists have noted that the neurodegeneration of A-T is not typical of other pure cerebellar degenerations, suggesting the potential contributions of extrapyramidal, brainstem, and peripheral nerve degeneration [1,3,176]. The severity of the neurological phenotype in A-T can thus be influenced by genes that function at several physiological levels, probably affecting different parts of the CNS. Identification of these genes is expected to identify new facets of the physiological pathways that lead from DDR defects to the associated clinical phenotype.

### 7. Conclusion

Our understanding of the vulnerability of the CNS to DDR defects has recently been expanded, not least by new insights into the neurological phenotype in A-T. It is becoming evident that the lack of ATM-mediated DDR in neurons underlies this phenotype, despite inevitable differences in the DDR between neurons and proliferating cells. Major questions about A-T awaiting answers concern these differences, the mode of cell death of DNA-damaged neurons, and the identification of the missing links in the physiological translation of CNS pathology to a clinical phenotype. Work in these directions is expected to pave new avenues to effective treatment of A-T patients.

### Conflict of interest

None.

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