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Review Article

ATM: Expanding roles as a chief guardian of genome stability

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Human morbidity and mortality is determined by the interaction between genetic factors, environment, life events and health behavior. An important genetic variable that affects people's health is the efficiency at which they maintain the stability and integrity of their genome. This parameter is collectively determined by genotypes at numerous genetic loci. DNA damage – a major threat to genome stability - is usually attributed to environmental DNA damaging agents. However, most of the ongoing damage that is continuously inflicted on cellular DNA is in fact caused by endogenous oxygen radicals produced in metabolism, inducing tens of thousands of DNA lesions per day

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[1–4]. Defense against this persistent threat on genome integrity is critical for cellular homeostasis, timely development, and prevention of undue cell death, cancer and premature aging [2,5–10]. This defense is provided primarily by the DNA damage response (DDR) – an extensive signaling network which responds to DNA lesions. The DDR activates DNA repair mechanisms and sets in motion numerous pathways, which rapidly modulate many physiological processes. The DDR is most vigorously activated by double-strand breaks (DSBs) in the DNA, and the DSB response is probably one of the most comprehensive signaling networks activated by a physiological stimulus [5,6,11–13]. The importance of the DDR in human health is highlighted by deleterious mutations which lead to "genome instability syndromes", usually characterized by progressive degeneration of specific tissues, cancer predisposition, chromosomal instability, and sensitivity to various DNA damaging agents [2,5,8,9,14–16]. A broader effect on public health is conferred by heterozygosity for mutations affecting certain DDR players such as BRCA1, BRCA2, PALB2, p53, and the mismatch repair proteins. Such genotypes result in predisposition to specific cancers, emphasizing the intimate link between the formation and progression of cancers and genome instability [7,10,15,17–22]. It is also becoming clear that differential maintenance of genome stability accounts for variation in aging and associated diseases in the general population [9,23]. The number of studies indicating a link between sequence variations in genes that are involved in genome stability, and human pathology and cancer therapy outcomes, is rapidly rising [24–28]. Thus, in addition to the extreme phenotypes observed in the genome instability syndromes, and the presumed embryonic death inflicted by very severe DDR defects, a continuum of chronic morbidity is very likely caused by the wide variation in DDR efficiency within a population.

Ataxia-telangiectasia and the ATM protein

Ataxia-telangiectasia (A-T) is an autosomal recessive genome instability disorder [16,29] caused by mutations in the *ATM* gene, which encodes the ATM protein kinase [30–32]. The hallmarks of this disease include severe neuromotor dysfunction, emanating primarily from progressive cerebellar atrophy, telangiectasia (dilation of blood vessels observed primarily in the eyes and occasionally on the facial skin), general immunodeficiency, thymic and gonadal degeneration, striking predisposition to malignancies - mainly lymphoreticular, extreme sensitivity to ionizing radiation and, in some patients, growth retardation, premature aging and insulin resistance. The cellular phenotype of A-T is characterized by increased chromosomal instability, premature senescence of cultured primary fibroblasts, and hypersensitivity to DNA damaging agents, particularly those that induce DSBs. This sensitivity results from a profound defect in the cellular response to DSBs. The chief mobilizer of this response is the ATM protein kinase, whose encoding gene is mutated in A-T patients [33,34].

DSBs can be induced by ionizing radiation, radiomimetic chemicals, or endogenous reactive oxygen species [35]. They also accompany physiological genome transactions such as meiotic recombination [36,37] and the rearrangement of antigen receptor genes in the adaptive immune system [38]. DSBs are ultimately repaired via nonhomologous end-joining (NHEJ) or homologous recombination repair (HRR) mediated by recombination between sister DNA molecules. These two DSB repair avenues can be divided to several subpathways (reviewed in Refs. [39–42]). However, DSB repair constitutes just one branch of the larger DSB response, which also activates special cell cycle checkpoints, moderates gene expression, alters protein turnover and activity, and modulates many other cellular circuits. This extensive network is based on a group of *bona fide* DDR players, but also temporarily recruits numerous players from other arenas of cellular metabolism, which usually undergo specific post-translational modifications (PTMs) in the DDR context [11,33,43–46]. The DSB response begins with *sensor/mediator* proteins which are rapidly recruited to the sites of damaged DNA, forming large structures at nuclear foci [47] in a finely regulated manner [11,43,47]. While chromatin is reorganized around the break site and the DSB ends are processed and prepared for repair, a signal - whose physical identity is yet unknown - is sent to the *transducers* - powerful protein kinases, which subsequently relay the signal to numerous downstream *effectors* that are involved in a multitude of pathways. The primary transducer of the DSB response network is ATM [12,34,48]. In response to DSB induction, ATM's activity is markedly enhanced. Full and timely activation of ATM is dependent on the MRE11-RAD50-NBS1 (MRN) complex – a major DSB sensor [49,50] – and is accompanied by a flurry of PTMs on the ATM molecule, including several autophosphorylations and acetylation [33,48,51–55]. Activated ATM then phosphorylates numerous players in various pathways of the DSB response [33,53,56–58]. Among these are some of the sensors, resulting in rapid amplification of the signal emanating from the DSB sites. ATM activates other protein kinases as well via their ATM-mediated phosphorylation, and these in turn phosphorylate their own targets. The end result is a multi-layered phosphorylation network [58]. ATM typically fine-tunes a downstream pathway by phosphorylating several players in it. Targeted proteins may undergo several ATM-dependent PTMs, some of them direct ATM-mediated phosphorylations and others carried out by enzymes activated in an ATM-dependent manner. One extensively documented such pathway is the stabilization and activation of the p53 protein in response to DSB induction (reviewed in Ref. [33]).

ATM belongs to a family of PI-3 kinase-like protein kinases (PIKKs) [59]. This family includes, among others, the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs), which is involved in the NHEJ pathway of DSB repair, but probably also in other genotoxic stress responses [60,61], and ATR, which responds primarily to stalled replication forks [13,62]. Evidence suggests a considerable degree of redundancy and collaboration between these three PIKKs, which preferably phosphorylate Ser or Thr residues followed by Gln (S/TQ motif) [11,13,43,59,63].

Importantly, while ATM's role in the DSB response is its most extensively studied function, ATM has recently emerged as a homeostatic protein kinase that is active in other stress responses and several metabolic pathways. Notable among them are maintenance of the cellular redox balance [64–67] (and see below), mitochondrial metabolism including maintenance of mitochondrial DNA [68–72]. Importantly, these functions of ATM involve different modes of ATM activation presumably directing ATM to different substrates [64,73] (and see below) Fig. 1.

Many A-T symptoms can be attributed to the abrogation of the cellular response to physiological DSBs and to DSBs induced by endogenous reactive oxygen species [34]. However, the cause of the most serious manifestation of this disease – the progressive cerebellar degeneration – is still being debated [74–78]. This debate is fueled by evidence that ATM's capacity as a protein kinase is also exploited in

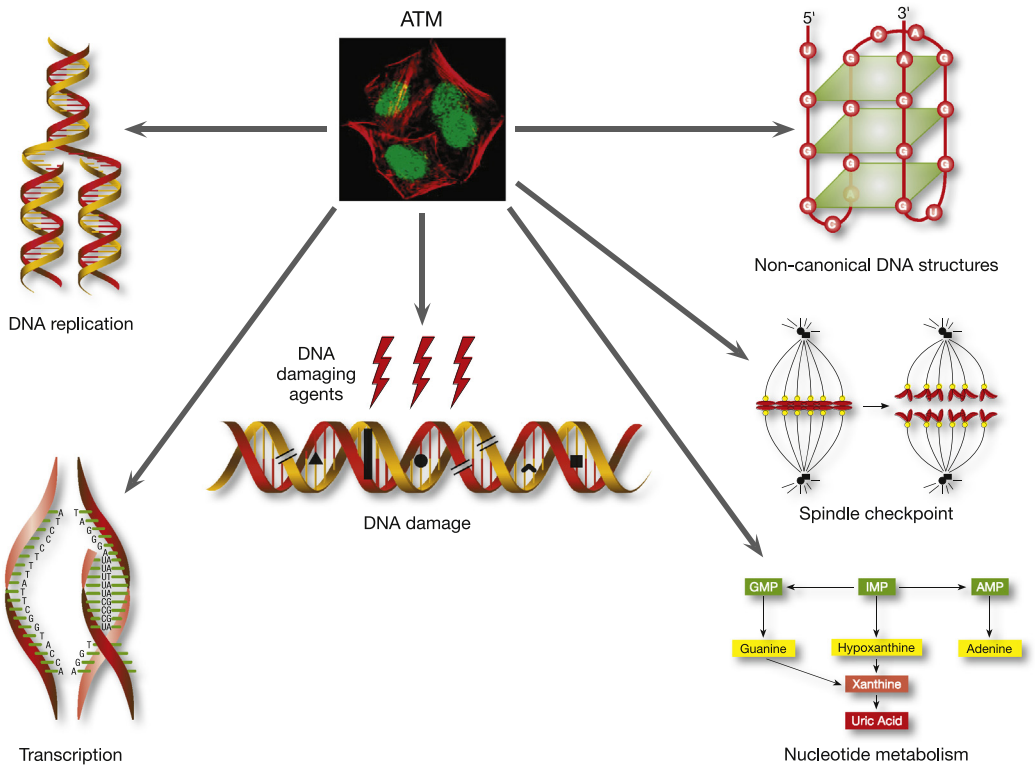

Fig. 1 – Involvement of ATM in protecting genome homeostasis during physiological processes and in response to DNA damage.

signaling pathways that are not associated with DNA damage, some of which are even cytoplasmic [64,66,68,71,79]. Investigators have suggested that the ATM functions whose loss is responsible for the cerebellar atrophy in A-T could be those that are associated with ATM's non-DDR roles [64,68,76,79–81]. We attribute this cardinal feature of A-T to the loss of ATM's comprehensive role in maintaining genome stability, which encompasses many aspects of genome integrity in addition to its well-documented role in mobilizing the DSB response. Importantly, while the *ATM* gene and its protein product were initially identified due to interest in the A-T phenotype [30], efforts to decipher this disease continue to spur and fertilize the endeavor to elucidate ATM's functions.

ATM and maintenance of genome stability: beyond the DSB response

The extreme radiosensitivity of A-T patients and of A-T cells attracted, right from the start, the attention of researchers as a potential clue to the underlying physiological defect in this disease - and rightly so. The subsequent recognition that the critical DNA lesion mishandled by ATM-deficient cells was the DSB, and the discovery of ATM's central role in the DSB response, seemingly made all the pieces fall together in the A-T puzzle. Concerns are expressed, however, about attributing the neurodegenerative aspects of A-T solely to the defective DSB response [78]. Indeed, several details were disregarded or played down along the road to understanding A-T: 1. The progressive nature of genome instability syndromes should be explained primarily by failure in coping with the ongoing DNA damage caused by endogenous agents and nucleic acid metabolism, and not by external DNA damaging agents such as those used in the lab. The daily damage inflicted upon DNA by "the enemy from within" involves mostly single-strand breaks (SSBs) and DNA base modifications, with DSBs actually being in the minority. This distribution is very different from that obtained in a laboratory setup using radiation and DNA damaging chemicals, which aims to intensify DDR readouts; 2. Sporadic reports describe varying degrees of sensitivity among A-T cells to different DNA damaging agents [82–97]. This suggests that a spectrum of deficiency exists amongst these cells in coping with a broad array of DNA lesions, not only DSBs. Similar observations were made during the course of our early studies about the sensitivity of A-T cells to DNA damaging agents [98–102] (and unpublished data). An example of documented ATM-mediated pathway in response to UV radiation is the stabilization of ribonucleotide reductase via ATM-mediated phosphorylation of its subunit, p53R2 [103]. Naturally, these observations were overshadowed by the striking defect in the DSB response of A-T cells, and were attributed to failure of A-T cells to cope with DSBs formed during repair of other lesions.

Is ATM involved in responding to DNA lesions other than DSBs? What is its mode of action in the cellular response to such lesions? ATM's ability to modulate the function, activity and stability of other proteins is based on their targeting by its kinase activity. Indeed, among ATM substrates which were studied in detail are proteins that respond to various DNA lesions or to structural aberrations in the DNA. Below are several examples. 1. The tight link between ATM and the Fanconi anemia pathway of crosslink repair, in which ATM phosphorylates several targets [104,105]; 2. ATM targets tyrosyl-DNA phosphodiesterase (TDP1) [106], which hydrolyzes the phosphotyrosyl bond in the cleavage complex between a DNA 3′ end and stalled topoisomerase I (Top1-CCs) [107]. TDP1 acts as a repair

enzyme in the response to SSB-associated Top1-CCs [107]. The importance of ATM in resolving Top1-CCs has recently been further pointed out [108,109]. Interestingly, in this pathway ATM was also found to play a role in ubiquitylation and degradation of stalled Top1 in a manner that was independent of ATM's kinase activity [109]. On the other hand, it was recently shown that ATM-mediated phosphorylation of the CtIP endonuclease is required for normal response to Top1 and Top2 poisons [110], hence ATM may apply its usual, multipronged approach to regulate the processing of topoisomerase-DNA cleavage complexes [107,111]; 3. ATM mediates phosphorylation of polynucleotide kinase 3′ phosphatase (PNKP) [112–114], which phosphorylates 5′-OH and dephosphorylates 3′-phosphate DNA ends that are formed at damaged DNA strand termini, thereby regenerating legitimate ends for further processing [115]. PNKP has been implicated in both SSB and DSB repair, and ATM-mediated phosphorylation enhances its catalytic activity and stabilizes it [112–114]; 4. ATM-mediated phosphorylation was found to enhance the activity of 3-methylpurine-DNA glycosylase (MPG). MPG is a key player in base excision repair – a central DNA repair pathway in the face of alkylating agents and DNA lesions induced by endogenous agents [116,117]. MPG is responsible for the initial recognition of several alkylpurines and carries out the first step in the repair of these lesions; 5. ATM mediates phosphorylation of the recQ helicase-like proteins BLM [118–121] and WRN (our unpublished data), enhancing their activity. The mammalian recQ helicases resolve complex DNA structures formed in recombination, repair and other aspects of DNA dynamics [122]. Beamish et al. [119], who described the functional interaction between ATM and BLM, concluded that "…ATM and BLM function together in recognizing abnormal DNA structures…".

Moreover, phosphoproteomic screens have shown that many repair enzymes that process various DNA lesions are phosphorylated on S/TQ sites in response to experimental DNA damage induction [53,56,57]. On one hand, these phosphorylations may represent the functional recruitment of players from various DNA repair pathways to the service of the DSB response. On the other hand, such phosphorylations may in fact reflect ATM's ability to modulate the activity of such players in their home turf – the repair pathways with which they are primarily associated.

Collectively, these observations suggest that ATM-mediated phosphorylations may have supporting roles in a variety of genotoxic stress responses and in resolving aberrant DNA structures that are occasionally formed during the course of DNA metabolism. This ongoing, low-profile role of ATM may represent a considerable portion of ATM's routine functions. ATM-dependent enhancement of these enzymes may serve to adjust their activity in the face of a local burst of DNA damage following a physiological stress. In such a scenario, ATM may assist in streamlining or fine-tuning the cellular response to various DNA lesions or abnormal structures by modulating the activity of the pertinent enzymes. ATM is likely not critical for these processes, but its loss may reduce their efficiency, particularly in situations where its assistance is advantageous. Genome stability is not affected only by DDR efficiency. If we take a broader look at this term, evidence will emerge for involvement of ATM in other aspects of "genome homeostasis": 1. The bilateral relationships and partial redundancy between ATM and ATR suggest that both are required for timely response to DSBs as well as in responding to replication stress [11,13,43,59,62,63]. Of note, ATM can be activated by hypoxia, which can lead to replication stress without initial DNA damage, but it is required to prevent subsequent accumulation of DNA damage under continuous hypoxia [123–126]; 2. ATM is clearly involved in telomere maintenance and dynamics. A-T cells have long been known to exhibit shortened telomeres and an excess of chromosome end fusions [127,128], and ATM was shown to interact physically and functionally with several proteins that protect and shape telomeres (reviewed in [129–131]). It was recently demonstrated that in neuronal cells, ATM and ATR cooperate in the response to uncapped telomeres [132]; 3. ATM responds directly to oxidative stress [64,67,73,133]. ATM activation by reactive oxygen species is not mediated by DNA damage or the MRN complex and involves a different mode of activation than that associated with DSBs, with a different ATM modification – generation of a disulfide-crosslinked ATM dimer ([73,133]. Oxidative stress plays a cardinal role in daily DNA damage. ATM's role in maintaining the cellular redox balance [64] may represent an important tier in its role as a shield of genome stability; 4. Additional MRN-independent modes of ATM activation by stresses, which do not induce DNA damage directly but may impact genome stability, are being revealed. Such are ATM activation by hyperthermia [134], by hypotonic stress, or by treatment with high salt or the chemical chloroquine [51], which affect chromatin organization. The latter mode of ATM activation is dependent on the nuclear zinc-finger protein ATMIN (ATM INteractor; also known as ASCIZ) [135]. This pathway is different and independent of the ATM activation triggered by DSBs, which is MRN-dependent, but a crosstalk between the two is maintained [136,137]. An important question is, whether different modes of ATM activation lead to ATM-mediated phosphorylation of different subsets of downstream substrates [134]. 5. ATM was found to affect the stability and activity of key enzymes in the *de novo* or salvage pathways of nucleotide synthesis, in response to induced DNA damage or endogenous stress [68,103,138]. In a phosphoproteomic screen carried out in our lab [53], the use of an ATM inhibitor showed that additional enzymes in nucleotide biogenesis were phosphorylated in an ATM-dependent manner. Regulation of the nucleotide pool impacts DNA metabolism and hence genome stability [139]. 6. ATM was implicated in regulation of the mitotic spindle checkpoint, which obviously impinges on genome stability [140–143].

In conclusion

Several molecules have been crowned in the past as ultimate "guardians of the genome", most notably, the p53 protein. Maintenance of genome stability is carried out by the ongoing, concerted action of numerous proteins, and this network is constantly modulated in the face of shifting challenges. Clearly, certain molecules, such as DDR transducers that are members of the PIKK family, play pivotal roles in maintaining genome homeostasis throughout the cell's life. ATM is emerging as a prominent sentry at the gate of genome integrity, by virtue of its ability to modulate numerous aspects of genome stability, probably via different capabilities. Its role as the chief mobilizer of the DSB response is likely the most intense manifestation of its power, which is expressed under extreme situations. This impressive demonstration of ATM's potential should not diminish its value as regulator of the many cellular responses to the daily wear and tear of the cellular genome.

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