

Invited review

Molecular basis of ataxia telangiectasia and related diseasesLindsay G BALL, Wei XIAO¹*Department of Microbiology and Immunology, University of Saskatchewan, Saskatoon, SK Canada, S7N 5E5.***Key words**

ataxia telangiectasia; DNA damage; DNA repair; cdc genes; phosphotransferases

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Abstract

Ataxia telangiectasia (AT) is a rare human disease characterized by extreme cellular sensitivity to radiation and a predisposition to cancer, with a hallmark of onset in early childhood. Several human diseases also share similar symptoms with AT albeit with different degrees of severity and different associated disorders. While all AT patients contain mutations in the AT-mutated gene (ATM), most other AT-like disorders are defective in genes encoding an MRN protein complex consisting of Mre11, Rad50 and Nbs1. Both ATM and MRN function as cellular sensors to DNA double-strand breaks, which lead to the recruitment and phosphorylation of an array of substrate proteins involved in DNA repair, apoptosis and cell-cycle checkpoints, as well as gene regulation, translation initiation and telomere maintenance. ATM is a member of the family of phosphatidylinositol 3-kinase-like protein kinases (PIKK), and the discovery of many ATM substrates provides the underlying mechanisms of heterologous symptoms among AT patients. This review article focuses on recent findings related to the initial recognition of double-strand breaks by ATM and MRN, as well as a DNA-dependent protein kinase complex consisting of the heterodimer Ku70/Ku80 and its catalytic subunit DNA-PKcs, another member of PIKK. This possible interaction suggests that a much greater complex is involved in sensing, transducing and co-ordinating cellular events in response to genome instability.

Ataxia telangiectasia clinical presentation

Ataxia telangiectasia (AT) is a rare human disease characterized by extreme sensitivity to radiation^[1–5]. AT is a progressive neurodegenerative disorder causing a predisposition to cancer, with a hallmark of onset in early childhood^[6–9]. AT is seen in approximately 1 in every 40 000 live births in the USA, although the frequency varies from country to country^[10]. At birth, infants appear normal and begin walking at a normal age (approximately age 1 year); however, by age 2–3 ataxia (loss of muscle co-ordination) becomes visible and generally by age 10 patients are confined to a wheelchair^[10]. Ataxia generally precedes telangiectasia, which is described as the chronic dilation of a group of capillaries causing elevated, dark red blotches on the skin or eyes^[11]. This disease is additionally characterized by cerebellar degeneration, and immune system defects^[12–14]. In younger children, diagnosis of AT is somewhat obscure as the cerebellum appears

to be of normal size for several years although onset of ataxia is prevalent. However, by age 10 magnetic resonance imaging (MRI) generally shows an abnormal cerebellum that has decreased in volume^[15]. Studies have shown a gradual decrease in granular and Purkinje cells, which are large branching cells of the nervous system and are located in the middle layer of the lower part of the brain, or the cerebellum^[14–16]. Unfortunately, there is currently no treatment for AT except for supportive therapy of secondary symptoms^[17].

In addition to an up to several hundredfold increase in developing certain types of cancers (eg lymphoma) in AT patients, epidemiological studies suggest that heterozygote AT mutation carriers are also at increased risk for cancer, particularly breast carcinoma^[18,19]. This is of great significance as it is estimated that approximately 1% of the population are AT carriers. However, it is noted that a recent study showed that heterozygous AT mutations did not confer genetic predisposition to early onset of breast cancer^[20].

Serum alphafetoprotein (AFP) levels are elevated in more than 95% of AT patients, which is therefore used to diagnose AT and to distinguish from AT variants^[4,5,10,21]. When dealing with AFP it is important to note that AFP levels are normally higher at birth than those at age 2, thus diagnostics for AT using AFP cannot be conducted until after the age of 2. There are known malignancies associated with AFP^[10,22]. For example, AFP is known to be elevated in case of spina bifida and anencephaly, and this elevation is the hallmark test for early detection of both conditions. Spina bifida is part of a group of birth defects called neural tube defects, which affect embryonic structures that eventually develop into the brain, spinal cord and tissues that enclose them. Anencephaly is a congenital condition in which portions of the brain fail to develop. Because AFP is such a diagnostic hallmark for AT, it is surprising that the mechanism of AFP upregulation in normal and AT cells has not been reported. Nevertheless, given the commonality of AFP elevation in all of the above 3 diseases, it is conceivable that the increased AFP level is responsible for the Purkinje cell degeneration in AT patients.

Ataxia telangiectasia-related diseases

There are several human deficiencies and diseases that are closely related to AT. For example, molecular cloning has now allowed for the distinction between AT and other autosomal recessive cerebellar ataxias (ARCA) such as Friedreich ataxia or A-T_{Fresno}, an old-fashioned term for an AT variant^[23–25], oculomotor apraxias 1 (aprataxin deficiency), oculomotor apraxias 2 (senataxin deficiency), aicardi syndrome and AT-like disorder (ATLD)^[26–29].

AT-like disorder is a very rare disorder with clinical features similar to those of AT, with the most prominent similarity being progressive cerebellar ataxia. However, ATLD patients that do not present with telangiectasia^[30,31], have a later onset of neurological features, slower progression, and thus milder symptoms compared to AT patients^[27].

Closely related to AT and ATLD is the Nijmegen breakage syndrome (NBS)^[23–25]. NBS and ATLD have some overlapping features such as hypersensitivity to ionizing radiation and genome instability, and both are characterized by neurological deficits^[32,33]. Thus, NBS was long considered as a clinical variant of AT. Clinical distinction has been made as NBS patients also present with a characteristic facial appearance and microcephaly as well as growth retardation^[34]. Clearly the above AT-related human conditions suggest deficiency at common cellular function(s) and genetic pathway(s) with AT.

Laboratory findings in ataxia telangiectasia and ataxia telangiectasia-related patients

Laboratory findings in patients with AT show: immunodeficiencies emerging as decreased IgA, IgE and IgG2 levels^[5,21,35–38], characteristic chromosomal aberrations and an increased rate of telomeric shortening^[39], radiosensitivity^[1–5], as well as sensitivity to other DNA damaging agents and non-DNA damaging agents^[40]. Chromosome instability, cell-cycle checkpoint defects^[3] and elevated serum levels of AFP^[21,22] are prevalent in most AT patient cells. In addition, approximately one-third of AT patients develop cancer, which is usually lymphoid^[10].

Both NBS and ATLD cells share a number of cellular phenotypes with AT cells, with the most prominent being the increased sensitivity to ionizing radiation, abnormal cell-cycle checkpoints, chromosome instability, immunodeficiency and accelerated shortening of telomeres^[41,42]. In particular, all 3 disorders show an increased level of chromosome translocation in the peripheral blood between the loci of the immunoglobulin and T-cell receptor genes on chromosomes 7 and 14^[43,44]. Hence, laboratory findings are most consistent with all 3 diseases belonging to a group of disorders referred to chromosome instability syndromes.

Molecular basis of ataxia telangiectasia and related diseases

AT is the result of mutations in the AT-mutated (*ATM*) gene, which was discovered in 1995^[45,46]. AT patients suffer as a result of over 400 distinct *ATM* mutations, of which 85% are accounted for by null mutations in the *ATM* gene^[21,47,48]. Thus, approximately 85% of AT sufferers have no detectable *ATM* protein^[21,48]. There are a few reported genuine AT cases with normal *ATM* protein levels; however, in these cases the protein is defective in *ATM* enzyme activity^[49,50]. The establishment of AT as a monogenetic disease assisted in efficient diagnosis and reevaluation of “AT variants”. The fact that some AT patients carry hypomorphic *ATM* mutations (ie mutations with partial functions) provides an underlying explanation for atypical AT patients with minimal signs of symptoms, such as very mild or late-onset of syndromes or a subset of disorders^[51].

The *ATM* protein is a member of the phosphatidylinositol 3-kinase-like family of serine/threonine protein kinases (PIKK)^[13,52]. It is thus grouped because all PIKK contain a conserved kinase domain initially reported in phosphatidylinositol 3-kinase. This family represents an atypical subclass of protein kinases responsible for phosphorylation of its substrates on serine or threonine followed by glutamine

(SQ or TQ)^[53-55]. The mammalian PIKK known to be involved in the DNA damage response are: DNA-PKcs (the catalytic subunit of DNA-dependent protein kinase), ATM (ataxia telangiectasia gene product), ATR (ATM and Rad3-related), mTOR/FRAP (mammalian target of rapamycin/FKBP-rapamycin-associated protein) and ATX/SMG1^[13].

The ATM protein is a fairly large (approximately 350 kDa) protein that can be divided into several structural and functional domains (Figure 1A). The first is an FAT domain, which is conserved among the PIKK family of proteins FRAP, ATR and TRRAP; the second is a phosphoinositide 3,4-kinase (PI3K) domain, which ATM has in common with DNA-PKcs; and the third is an FAT carboxy-terminal domain (FATC)^[56]. In addition, the amino terminus of the ATM protein contains multiple HEAT (huntingtin, elongation factor 3, A subunit of protein phosphatase 2A and TOR1) repeats^[57]. A recent solution structure analysis of the FATC domain^[58] revealed an α -helix and a disulfide-bonded loop that undergoes conformational changes. Hence, the FATC domain may regulate protein activity and stability. The precise function of HEAT repeats is currently unknown, although it is speculated to be involved in the interaction with other proteins, as these repeats are anti-parallel α -helices linked by a flexible loop^[40,57].

The overall shape of ATM is very similar to DNA-PKcs and is comprised of a head and a long arm that is thought to wrap around double-stranded DNA after a conformational change^[59-63]. One of the hallmarks of the ATM protein is its rapid increase in kinase activity immediately following exposure to ionizing radiation (IR), or in the presence of double-strand breaks (DSB)^[64,65].

The gene mutated in NBS was identified as *NBS1*^[25,66,67] whereas ATLD is caused by mutations in the *MRE11* gene^[29]. Unlike AT, which can result from complete inactivation of the coding gene, all NBS and ATLD patients carry hypomorphic mutations that express some level of corresponding protein, either truncated or full length with amino acid substitutions^[27,68]. Indeed, attempts to create null *Mre11* mutations in mouse embryonic stem cells has failed and conditional knockout experiments demonstrated that this gene is required for normal cell proliferation^[69], suggesting that *MRE11* is an essential gene in mammals. Similarly, complete *Nbs1* knockout mice are embryonic lethal^[70,71]. This assertion is further confirmed by a report that disruption of mouse *Rad50*, encoding the third component of the MRN (MRX in yeast) complex consisting of Mre11, Rad50, and Nbs1 (aka nibrin and p95; Xrs2 in yeast), also causes embryonic stem

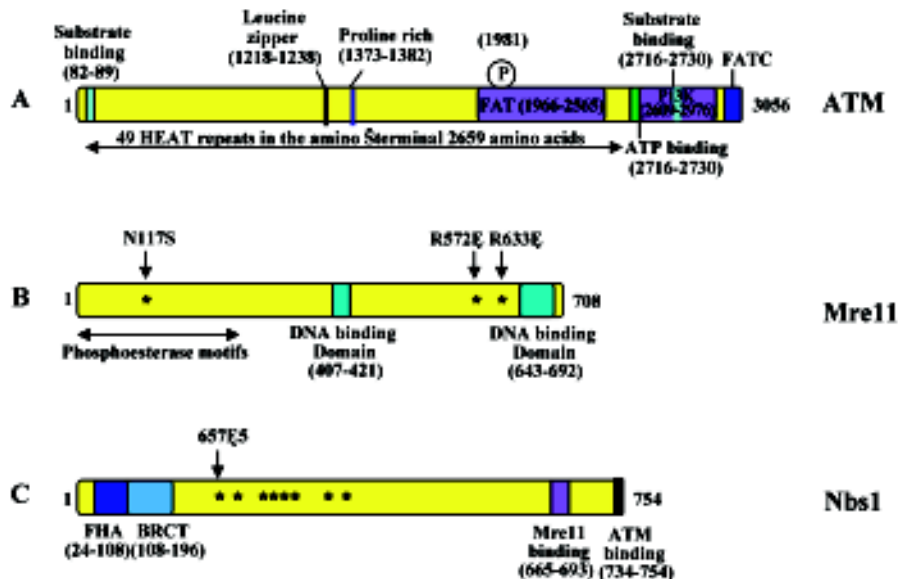


Figure 1. Schematic representation of the ATM, Mre11 and Nbs1 proteins. (A) ATM and its functional domains. Most domains have been discussed in the text. The letter “P” indicates the phosphorylation site required for its activation. (B) Mre11 and its functional domains. The asterisks represent the known mutations that cause ataxia telangiectasia-like disorder (ATLD). Note that only two families of ATLD with *MRE11* mutations were reported. One is homozygous for the mutation C1897T, resulting in R633 Δ (stop codon), whereas the second family is heterozygous for A350G (N117S) and C1714T (R572 Δ). (C) Nbs1 and its functional domains. The asterisks indicate the known *NBS1* mutations that cause Nijmegen breakage syndrome (NBS), among which the homozygous 657 Δ 5 mutation accounts for over 90% of NBS patients. 657 Δ 5 contains a 5-bp deletion, resulting in a truncated 26 kDa protein with only forkhead-associated (FHA) and BRCA1 C-terminus (BRCT) domains. Other *NBS1* mutations cause various degrees of symptoms.

cell lethality^[72].

The human *MRE11* gene was initially isolated by its possible protein interaction with DNA ligase I^[73] and was predicted to encode a 708-amino acid protein. However, subsequent reports appear to favor an Mre11B sequence (Figure 1B), which is different from Mre11 primarily at the C-terminal region and significantly strengthens its similarity with Mre11 from other species^[74]. Mre11 contains a phosphoesterase motif at the N-terminal region that is highly conserved among all eukaryotic Mre11 and a similar motif is also found in *Escherichia coli* SbcD^[75]. It also contains DNA-binding domains at the C-terminal region and region(s) for homodimerization^[76,77]. Structural analyses^[78–80] indicate that the MRN complex consists of two molecules of Mre11 and Rad50 (an *E. coli* SbcC homolog) forming a rope-and-hook structure capable of bridging two DSB ends. *In vitro* characterization of the Rad50–Mre11 complex^[76,81–84] demonstrates that it possesses 3′ to 5′ exonuclease and single-strand endonuclease activities, as well as ATP-dependent DNA binding and limited unwinding activity.

The phenotypic similarity between NBS and ATLD patients is attributed to the fact that both corresponding proteins are components of the MRN complex. Mre11 interacts with both Rad50 and Nbs1/Xrs2, and its homodimerization or self-interaction appears to be important for the Mre11–Rad50 and Mre11–Nbs1/Xrs2 interactions^[76,77]. Interestingly, deficiency of the Mre11 protein results in decreased cellular levels of Nbs1 and Rad50, suggesting that the MRN complex is required for protein stability. The primary cellular function of MRN is a sensor for DNA strand breaks and to activate signaling pathways leading to cell-cycle checkpoint and recombination repair^[32,85,86]. While Mre11 and Rad50 are highly conserved in eukaryotes, from unicellular yeasts to human cells^[87,88], the third component, Nbs1, is less conserved structurally among eukaryotes, although the mammalian Nbs1 and yeast Xrs2 play similar roles within their respective MRN/MRX complex. Nbs1 has been suggested to be a regulatory subunit of MRN that is essential for Mre11 phosphorylation upon DNA damage^[89] and its biochemical activities, such as ATP-dependent DNA unwinding and nuclease activity^[90]. Although Nbs1 or Xrs2 is not required for the Mre11–Rad50 enzymatic activity *in vitro*, its activity appears to be absolutely required for MRX activity *in vivo*, as inactivation of any 1 of the 3 genes in yeast cells leads to complete loss of the MRX activity and indistinguishable cellular phenotypes^[91–93]. This essential function of Nbs1/Xrs2 is probably due to its role in recruiting ATM/Te11^[94]. The Nbs1 protein has 4 known functional regions: the N-terminal forkhead-associated (FHA) domain followed by a

BRCA1 C-terminus (BRCT) domain, a C-terminal Mre11-binding domain and an ATM-binding domain at the extreme C-terminus (Figure 1C). Interestingly, over 90% of all NBS patients analyzed to date contain a homozygous 5 bp truncating mutation, 657Δ5^[25], resulting in the production of a 26-kDa protein with FHA and BRCT domains but lacking the Mre11-binding domain (Figure 1C). Knockout mice producing similar truncated Nbs1 proteins are viable and develop symptoms characteristic of the human disease^[95,96], thus providing an animal model suitable for NBS research.

Phenotypic manifestation of genetic defects in ataxia telangiectasia and related diseases

One of the hallmarks of the ATM protein is its rapid increase in kinase activity immediately following DSB formation^[64,65], and its kinase activity remains its only known function to date. The phenotypic manifestation of AT is due to the broad range of substrates for the ATM kinase, as compiled recently^[40], involving DNA repair, apoptosis, G₁/S, intra-S checkpoint and G₂/M checkpoints, gene regulation, translation initiation, and telomere maintenance. Protein phosphorylation and de-phosphorylation is an important cellular regulatory mechanism that governs protein activity, stability, subcellular location and complex formation. We propose that although the primary ATM kinase substrates appear to be related to cellular response to DNA damage, novel ATM substrates and subsequent effects may explain all observed syndromes of AT patients, including elevated AFP level. We also propose that the multiple HEAT repeats in ATM may serve as a platform to interact with various regulatory and substrate proteins and to control its kinase activity in the aftermath of DNA damage. For example, the increased risk for breast cancer in AT patients has been implicated by the involvement of ATM in the interaction and phosphorylation of BRCA1 and its associated proteins following DNA damage^[97,98].

The ATM protein also has the ability to interact with the ends of double-stranded DNA^[99]. A recent model suggests that ATM is in an inactive dimeric or polymeric configuration, in which the kinase domain of each molecule is blocked by the FAT domain of the other^[100]. Following DNA damage, each ATM molecule phosphorylates the other on a serine residue at position 1981 within the FAT domain and thus converts into fully active monomers. It was shown that protein serine-threonine phosphatase 5 (PP5) is required for the activation of ATM and its subsequent kinase activity^[101].

The symptom similarity among AT, ATLD and NBS is apparently due to physical and genetic interactions between

ATM and MRN. Experimental results suggest that the ATM-MRN interaction in response to IR is complicated. First, the histone H2A isoform H2AX is rapidly phosphorylated (within 5 min) after irradiation in an ATM-dependent manner^[102,103], and the phosphorylated gH2AX interacts with MRN via the FHA/BRCT region of Nbs1^[103]. This interaction has been deemed indispensable for the recruitment of MRN^[41]. Second, in response to IR, ATM phosphorylates Nbs1 *in vivo*^[104], which is required for the subsequent phosphorylation of Mre11. Finally, phosphorylation and activation of the S-phase checkpoint effector Smc1 by ATM requires phosphorylated Nbs1^[105,106]. The above observations suggest that ATM acts upstream of MRN and is required to recruit MRN to the damage sites observed as distinct nuclear foci. On the other hand, MRN/MRX is known to bind DSB ends and a careful choreographic analysis in yeast^[107] indicates that MRX localization to nuclear DSB foci precedes and is required for that of Tel1, a yeast ATM ortholog^[108,109]. In mammalian cells, Mre11 appears to be required for ATM activation as well^[110], and this interaction was further reinforced very recently by an *in vitro* experiment showing that the MRN complex acts as a DSB sensor for ATM and recruits ATM to broken DNA molecules^[111]. Interestingly, the unwinding of DNA ends by MRN appears to be essential for ATM stimulation^[111], indicating that the MRN enzymatic activity plays a role in this process. In addition, a recent study^[112] shows that NFB1/MDC1, which interacts with MRN, is required for ATM activation under certain conditions. Alternatively, NFB1/MDC1 may help to recruit substrates, including Nbs1^[113,114], to ATM^[113-123]; suppression of NFB1/MDC1 leads to decreased ATM activation and decreased phosphorylation of ATM substrates^[112]. These observations support an assertion that MRN plays a crucial role in ATM phosphorylation of other substrates in response to DSB. The argument that MRN functions upstream of ATM is further strengthened by a very recent report that the extreme C-terminal 21 amino acid peptide of Nbs1 is required and sufficient for the interaction with ATM *in vivo* and *in vitro*, and that this interaction mediates ATM deposition to the sites of DNA damage and its checkpoint functions^[94]. The above genetic and physical interactions between MRN and ATM underlie the molecular basis for the shared cellular functions in cell-cycle checkpoints and recombination repair of DSB, as well as common syndromes among AT, ATLD and NBS.

DNA-PK: a missing link?

Despite the great advances made in the past decade re-

garding AT research, many questions remain to be answered. One question that remains unsolved is the involvement of Ku70/Ku80 in ATM-mediated cellular events in response to DSB. Ku70 and Ku80 form a heterodimer as DNA end-binding subunits of DNA-PK^[59-62]. It would be plausible to suggest that Ku70/Ku80 may also assist ATM's translocation to DSB, as Ku70/Ku80 is known to play such a role for DNA-PKcs, another member of PIKK with overall structural similarity to ATM^[124]. Like ATM, DNA-PKcs recognizes the same consensus phosphorylation sequence SQ/TQ, and also undergoes DSB-induced autophosphorylation, which is required for DSB repair^[125]. In addition, inactivation of either DNA-PK or ATM results in immunodeficiency; the former results in defective V(D)J recombination that leads to *scid* (severe combined immune deficiency) mutations^[126,127], whereas the latter results in the disruption of immune gene rearrangement^[128]. We propose that in the presence of Ku70/Ku80, DNA-PKcs and ATM may undergo conformational changes to be suitable for the suggested role of further wrapping around DNA^[59-63]. Indeed, recent electron microscopy-based structural analyses of both DNA-PKcs^[129-131] and ATM^[63] suggest a similar architecture consisting of a "head" and a "palm" domain connected by an "arm". The palm domain binds DNA, which induces conformational changes and triggers an interaction between initially distant palm and head regions^[130]. These DNA-induced conformational changes alter the catalytic core and regulate the kinase activity^[131]. The difference between DNA-PKcs and ATM is that DNA-PKcs is activated in G₁ and is required for non-homologous end joining (NHEJ) and apoptosis if DNA damage is excessive^[132], while ATM is activated in S and G₂ phases and is required for S-phase checkpoint and homologous recombination (HR)^[40].

Another connection between ATM and Ku70/Ku80 is that yeast MRX is not only required for DSB signaling and HR, but also works with Ku70/Ku80 for NHEJ^[133-136] and telomere maintenance^[77,93,137,138]. The budding yeast *Saccharomyces cerevisiae* predominantly employs HR to repair DSB over NHEJ. On some occasions when DSB repair can be processed by either process, NHEJ was shown to precede HR^[139]. A compiled model can be proposed in which the telomere acts as a repository for Ku proteins, which relocate to DSB after DNA damage^[140] and recruit MRX^[141]. MRX can assist to recruit and activate Lif1 and Dnl4^[142], resulting in ligation of the broken ends. However, in budding yeast, the MRX complex most likely initiates 5' to 3' end resection^[76], hence committing to repair by HR. This commitment is probably due to the broken DSB ends that are unsuitable for direct ligation, or to the recruitment of Tel1 by MRX that

activates cell-cycle checkpoints and subsequent recruitment of other HR proteins^[107]. A similar regulatory cascade may also exist in higher eukaryotes; however, because mammalian cells have an extended G₁ phase, the initial DSB binding by Ku70/Ku80 may stimulate NHEJ more frequently than in yeast. In addition, mammalian cells contain 3 major PIKK family proteins, namely ATM, ATR and DNA-PKcs, involved in different modes of DNA repair and overlapping signal transduction in response to DNA damage. The mechanism of their recruitment to sites of DNA damage is conserved via a newly discovered motif^[94]. For example, ATR is recruited to a single-stranded DNA by ATRIP (ATR-interacting protein)^[143,144], whereas DNA-PKcs and ATM are recruited to DSB by Ku70/K80 and MRN, respectively. Based on the above observations, we have proposed a working model of cellular response to DSB in mammals, as presented in Figure 2.

Finally, the physical and functional interactions among Ku, MRN/MRX and ATM/Tel1 can also be found in telomeres. Both yeast^[145] and human^[146] Ku is bound to

telomeric DNA and protects its 3' overhang. The MRX complex in budding yeast is also associated with telomeres, and mutants deficient in Ku or MRX activity exhibit telomere shortening^[137,147]. Similar phenotypes are also observed in their homologous mutants in fission yeast and plants^[148-150]. Tel1 works together with MRX by either regulating the access of telomerase to the DNA end^[151], and/or preventing telomere end-to-end fusion^[152]. Tel1 is activated by the MRX complex and in turn phosphorylates MRX^[153], suggesting functional conservation between yeast and mammals. However, unlike Tel1, ATM has not been implicated in telomerase access to the telomere. Nevertheless, AT patient cells were shown to have shortened telomeres^[39,154], as well as other telomere abnormalities^[155,156]. Furthermore, transgenic mice defective in both ATM and telomerase dramatically increase telomere dysfunction compared to single mutants^[157], suggesting roles of ATM in telomere maintenance. The telomeric functions of ATM may be related to some symptoms of AT patients.

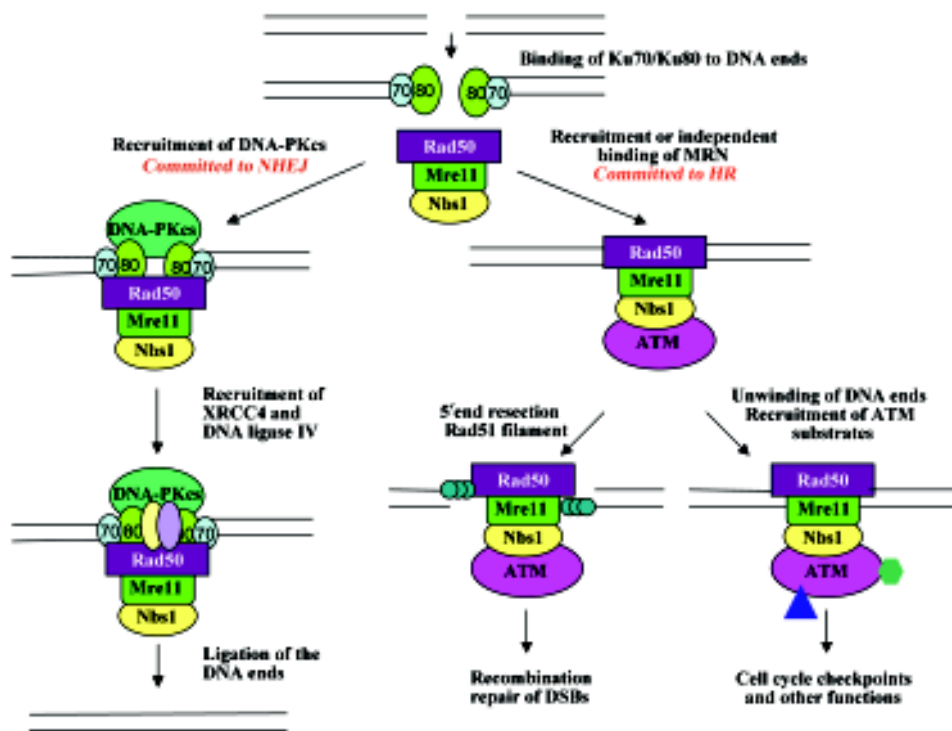


Figure 2. A proposed model for cellular response to DNA double-stranded breaks (DSB) in mammalian cells. The Ku70/Ku80 heterodimer binds to the broken DNA ends first, followed by the recruitment or the independent binding of the MRN complex (consisting of Mre11, Rad50 and Nbs1). If DNA-PKcs is recruited by interacting with the C-terminus of Ku80, cells are committed to non-homologous end joining. On the other hand, if ATM is recruited by interacting with the C-terminus of Nbs1, Ku70/Ku80 may be released and cells are probably committed to homologous recombination repair. Recruitment of ATM also leads to substrate phosphorylation and cell-cycle checkpoints. It should be noted that MRN may also bind to DNA ends without the assistance of Ku70/Ku80. Recent literature suggests that unwinding of DNA ends by MRN activates ATM and cell-cycle checkpoints, whereas DNA end resection by MRN initiates homologous recombination. The 2 processes may be co-regulated.

Conclusions

Since the initial discovery of the AT mutated gene 10 years ago, knowledge regarding the molecular mechanisms of AT and its related diseases has accumulated rapidly. It is now clear that the primary function of ATM and MRN, which is related to NBS and ATLD, is to respond to DNA damage, especially DSB. Two primary activities are cell-cycle checkpoint and DNA repair through HR, and these are achieved mainly via protein phosphorylation of various substrates, including ATM and MRN themselves. ATM and MRN are also involved in telomere maintenance and protection from chromosomal translocation, as well as efficient immune gene recombination. Although these cellular phenotypes are able to explain most phenotypes observed in AT and AT-related disease, some other associated symptoms may be due to diverse ATM substrates, unique MRN functions not shared by ATM, as well as the hypomorphic nature of the disease. Despite great advances in research, many questions remain to be answered especially with regard to treatment. Future efforts shall be directed to translational research for the cure and prevention of AT its and related diseases.

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