Chapter

The Role of the DNA Damage Response in Ataxia-Telangiectasia Syndrome

Albert Ribes-Zamora

Abstract

The DNA damage response (DDR) is a concerted response involving a myriad of pathways that cells elicit in the presence of DNA injuries. Patients bearing mutations in DDR genes have an increased cancer incidence derived from their diminished ability to respond to DNA damage, and the consequent increase in mutations. Intriguingly, mutations in ATM, the chief DDR regulator, can cause ataxia telangiectasia, a neurodegenerative disorder characterized by progressive loss of movement coordination, weak immune system, and increased cancer risk. The relationship between ATM and neural system development and degeneration remains to be fully elucidated and will be discussed in this chapter.

Keywords: ATM, DNA damage response, ataxia telangiectasia, neurodegeneration

1. Introduction

Mammalian cells face an estimate of 10^5 genomic injuries every day. These lesions are diverse and can include, among others, single (SSB) and double strand breaks (DSB), oxidative damage, DNA inter- and intra-strand crosslinking, base mismatches, bulky adducts, and photoproducts [1, 2]. This large variety of DNA lesions is directly related to the full range of mutation-causing agents that threaten the genome on a daily basis. Some of these agents are endogenously produced by the cell's own metabolism and homeostasis, while others are generated exogenously. The frequency of appearance of these lesions is also diverse, and it may depend on the cell type or the developmental stage [1]. For instance, skin epithelial cells are much more susceptible to photoproducts caused by ultraviolet rays, an exogenous source of mutations that can only reach the outermost layers of our body. In contrast, reactive oxygen species (ROS) are endogenous metabolic byproducts that can induce oxidative base modifications and SSB, one of the most common genomic injuries. Cells with high energy and metabolic demands are, therefore, most susceptible to suffer SSB-related and other ROS-related injuries.

To defend from the menacing threat that this wide range and number of lesions pose to the integrity of their genome, cells can invoke the DNA damage response (DDR), a vast network of overlapping pathways that is capable of tailoring a response depending on the type and extent of the lesion and the cell cycle stage at the moment of the injury [3–6]. DDR requires the coordination of DNA repair pathways with cell cycle progression regulation, transcription activation, and apoptosis, among other pathways [5, 7, 8].

Somewhat surprisingly, mutations in genes belonging to DDR pathways correlate with neurodevelopmental defects and neurodegenerative pathologies [5, 9–11]. For instance, individuals with dysfunctional versions of SSB repair genes APTX, PNPK, or XRCC1 manifest different types of ataxias with ocular apraxia; whereas, defective TDP1, also involved in SSB repair, can cause spinocerebellar ataxia with axonal neuropathy [9, 12]. Similarly, mutations in DSB repair gene MRE11, or central DDR regulators ATM and ATR, can lead to cerebellar ataxia [5, 13]. Besides ataxias, microcephaly is commonly found linked to defects in several DDR associated genes [1, 5, 14]. Mutations in NBS1 and RAD50, two genes involved in end processing during DSB repair, can cause Nijmegen breakage syndrome (NBS) and NBS-like syndrome, respectively, both syndromes manifesting microcephaly among other conditions [5, 15, 16]. Microcephalia is also present in individuals with dysfunctional PNPK, LIG4—a gene involved in DSB repair—or Seckel Syndrome 1, a developmental disorder caused by some ATR mutations [9, 15]. Furthermore, around 25% of patients with defective nucleotide excision repair (NER)—a DDR pathway in charge of healing photoproducts created by UV light exposure—can also present microcephaly among other neurological problems [5]. Overall, this data suggest a strong and intriguing link between DDR, neurodevelopment, and neuropathology. This review focuses on ATM, its role during DDR, and the molecular basis of ataxia-telangiectasia (A-T), a neurodegenerative syndrome caused by defective or absent ATM.

2. ATM roles during DDR

ATM and ATR are two kinases belonging to the protein phosphatidylinositol-3-kinase-like kinases (PIKK) family that function as the chief regulators of DDR [3, 11, 13]. Together, they coordinate all pathways implicated in DDR to offer an adequate and timely response proportionate to the type and extent of the genomic injury. Recently, DNA-PKcs, another member of the PIKK family, has also been found playing more substantial roles in regulating DDR than initially thought, albeit to a lesser extent that ATM and ATR [17].

ATM is a very large kinase of 3056 amino acids and a molecular weight of 350.6 kD that resides in the nucleus as inactive homodimers. Upon DNA damage infliction, phosphorylation of a critical ATM residue disrupts dimerization, prompting monomers to undergo further phosphorylation to achieve full kinase activation [18–20]. Active ATM monomers phosphorylate substrates on serine or threonine residues followed by glutamine (S/TQ), and a significant amount of ATM substrates contain clusters of S/TQ sites in short stretches of the protein [21]. These so-called SCD domains can be used to mine the proteome for putative ATM targets [22–24]. Using mass spectrometry, a high-throughput screen for proteins phosphorylated following DNA damage found 686 putative DDR targets and the final number is estimated to surpass a thousand proteins [25]. These large numbers showcase the complexity of DDR, and the need for an orchestrated coordination of all pathways involved. Some of the most important direct ATM targets are CHK2 and p53, two downstream effectors that modulate pivotal DDR pathways like cell cycle progression regulation, DNA repair, or apoptosis [26–28].

2.1 DNA repair

ATM is not only activated by different kinds of DNA damage but can also actively participate in several DNA repair mechanisms and coordinate their activities with other DDR-related pathways [7, 29]. During DSB repair, ATM

plays crucial roles in the early end-processing events, signal amplification, and recruitment of other DNA repair proteins to the sites of damage [3, 13]. ATM functions in homologous recombination (HR) and nonhomologous end-joining (NHEJ), the two pathways entrusted by cells to repair DSBs. Whereas, NHEJ is active throughout the cell cycle, its function is mostly limited to G0/G1 as S/G2 phases prefer the more accurate HR, a mechanism that uses sister chromatids only present during those phases as repair templates. The first sensor of DSBs is PARP1, which in addition to binding breaks, also adds branches of poly-(ADP)-ribose to proteins post-translationally [30]. This so-called PARylation process activates and recruits several DNA repair proteins to the sites of damage [31]. One of them is the MRN complex—made up of MRE11, RAD50, and NBS1—that binds and activates ATM [32, 33]. Interaction with PARP1 and NBS1, thus, activates and recruits ATM to DSB sites, where it phosphorylates several downstream targets and effectors to amplify DDR signaling. For instance, ATM phosphorylates histone variant H2AX, which promotes MDC1 binding to the chromatin surrounding DSB [34–36]. Once there, ATM-mediated phosphorylation of MDC1 promotes its binding to MRN, and recruitment of more ATM to phosphorylate more H2AX, further spreading DDR signaling [13].

Although the complete process remains to be fully elucidated, it is clear that ATM is also involved in the decision-making process that selects either HR or NHEJ to repair a DSB [37, 38]. A crucial step in this process is the extent of end resection that takes place at DSB [39]. ATM directly phosphorylates CtIP and BRCA1, two HR proteins required for resection initiation and binding of RAD51 to ssDNA ends, respectively [40–42]. Once formed, RAD51 coated 3′ ssDNA ends steer repair toward HR by initiating strand invasion into the sister chromatid. Intriguingly, ATM phosphorylates p53BP1 and promotes its recruitment to sites of DNA damage [43]. Phosphorylated p53BP1 has opposing roles to CtIP and BRCA1, and favors the formation of p53BP1 containing complexes at DSB that counteract HR in favor of NHEJ repair [38, 44]. ATM also influences NHEJ by mediating DNA-PKcs phosphorylation and subsequent recruitment of Artemis, an end-processing nuclease, to DSB sites [45].

Although ATM is mostly activated by DSBs, recent data suggest that some lesions that are usually repaired by BER can also activate ATM and that ATM-dependent phosphorylation events can regulate BER [46]. Following base damage, BER requires the sequential action of DNA glycosylases—to remove damaged bases and create apyrimidinic or apurinic (AP) sites, PARP1—to PARylate the AP site, and endonucleases that will generate an SSB at the AP site [47]. These events can lead to ATM activation and the ATM-dependent phosphorylation of CHK2 [46]. Upon activation, CHK2 phosphorylates XRCC1, a BER protein required for sealing the nick and completing the repair.

DDR is capable of modulating DNA repair pathways through multiple effectors. For instance, both ATR and p53 regulate NER through quite distinct mechanisms. While ATR phosphorylates XPA, one of the earliest respondents to pyrimidine photodimers and other bulky lesions, DDR-dependent phosphorylation of p53 acts by upregulating expression of NER genes and recruiting XPC and TFIIH to sites of damage [7, 48–52]. ATR also regulates ICLR through the phosphorylation of several members of the Fanconi anemia group, a set of proteins that in combination with NER and HR, repair DNA cross-linkage damage [53–55]. Other examples of DDR-signaling-dependent regulation of DNA repair mechanisms include the upregulation of BER through the stimulatory binding of p53 to BER proteins, the promotion of HR that ensues after disruption of the p53-RPA complex by ATM, ATR and DNA-PKcs phosphorylation, and the PIKK-dependent phosphorylation of Werner syndrome and Bloom syndrome proteins involved in DSB repair [56–60].

2.2 Cell cycle progression regulation

One of the most dangerous threats of DNA damage is the possibility of spreading to daughter cells during cell duplication. To prevent this, DDR is capable of halting cell cycle progression at any point during the cell cycle [61]. A series of overlapping mechanisms ensure that cells attempt DNA repair before progressing to the next cell cycle stage [7].

ATM is in charge of preventing lesions produced during G1/G0 to enter S phase, which is particularly important for some of the most common DNA injuries like oxidative damage. Since G1/G0 duration is usually longer than other cell cycle phases, exposure to ROS and other mutating agents is also higher in these stages, and so is the appearance of related damage. ATM acts in conjunction with CHK2 and p53 to block G1/S transition by inhibiting CDK2, the cycle-dependent kinase that along with Cyclin E, triggers S-phase entry [62]. CDK2 inhibition is achieved by two overlapping mechanisms that have ATM at their apex. On one hand, ATM phosphorylation of CHK2 triggers phosphorylation of CDC25A, a phosphatase required for CDK2 activation and promoting entry into S-phase [63, 64]. On the other hand, ATM-dependent activation of p53 induces upregulation of p21, which acts as a CDK2 inhibitor [65].

Replicative stresses during S-phase trigger the activation of the Intra-S-phase checkpoint to ensure that replicative stress and other types of damages do not persist in the following cell cycle stages. ATR, not ATM, is the PIKK responsible for halting the cell cycle at this stage through the activation of the intra-S-phase [61]. During this checkpoint ATR, CHK1, and p53 act together and in overlapping ways to phosphorylate CDK2, which renders it unable to form an active CDK2/cyclin A complex [63, 66]. The final result is DNA synthesis termination, premature stalling, and subsequent halt of the cell cycle.

The concerted action of ATR, CHK1, and p53 also controls the G2/M transition to ensure that no cell enters mitosis with lingering DNA damage from previous phases [67–69]. The importance of this checkpoint is highlighted by the presence of multiple overlapping and complementary mechanisms actively working together to inhibit CDK1/CyclinB1, the complex required to trigger entry into mitosis [66]. CDK1 phosphorylation has an inhibitory effect and thus, is the primary target of several of these mechanisms. After ATR-mediated activation, CHK1 phosphorylates CDC25C, a phosphatase required for CDK1 activation. Phosphorylated CDC25C binds to the 14-3-3 complex, which promotes its transport to the cytoplasm, effectively preventing CDK1 activation [70]. Active CHK1 also phosphorylates and activates WEE1, a kinase that promotes inhibitory phosphorylation of CDK1 [71]. Furthermore, ATR phosphorylates PLK1 and inhibits its role as WEE1 inhibitor, while p53 upregulates GADD45, which binds and further inhibits CDK1/CyclinB1 complex [72, 73]. Importantly, ATM also play roles in this combined effort to keep CDK1/CyclinB1 inhibited, as it can phosphorylate PLK1 and promote CHK1-mediated CDC25C phosphorylation [73, 74].

Finally, the Intra-M checkpoint is the last opportunity to prevent the transmission of damage to daughter cells. ATM and CHK1 govern this checkpoint through two distinct mechanisms that act sequentially during mitosis progression. First, inhibitory phosphorylation of PLK1 by CHK1 prevents it from acting during spindle formation and halts the cell cycle [74]. At a later point, ATR-mediated phosphorylation of Aurora B stimulates the inhibitory effect that this enzyme exerts over cytokinesis and delays exits of mitosis if the damage is detected [75].

2.3 Transcription regulation

Activation of DDR induces substantial changes to the transcriptome to equip cells with necessary tools and time to articulate a proper response. While the overall effect

of DDR activation is an attenuation of global transcription and translation, many genes involved in DDR pathways must be upregulated instead [76]. For example, upregulation of XPC and other NER genes follows DDR activation, and as previously noted, DDR-mediated blocking of cell cycle progression is dependent on the induction of certain genes, namely p21 [77]. DDR exerts its influence on gene transcription through the action of several transcription factors that act as downstream effectors of DDR signaling. Some of the most important examples are p53 and BRAC1, AP-1, or E2F1. For instance, BRAC1 and p53 upregulate XPC during DDR-mediated NER upregulation; whereas, AP-1 induces the expression of XPF and XPG during the same process [76]. Other examples are p53 and AP-1 serving as transcription factors for MLH1 and MSH2—two mismatch repair genes—and E2F1 and AP-1 influencing the expression of BER components XRCC1 and APEX1, respectively.

2.4 Apoptosis and senescence

Paramount for DDR is its ability to trigger apoptosis when DNA damage is too extensive and incompatible with genome stability. Both ATM and ATR can promote apoptosis through the phosphorylation of p53, the chief regulator of apoptosis during DDR [78–80]. p53 can trigger apoptosis by playing dual roles as transcription factor activator and anti-apoptotic protein inhibitor. In the presence of unrepairable damage, p53 upregulates pro-apoptotic genes like PUMA or BAX, while binding and inhibiting anti-apoptotic proteins like BCL2 [81, 82]. In addition to apoptosis, extensive DNA damage can also induce senescence, a metabolic state that causes irreversible growth arrest [83]. Among other mechanisms, senescence can be induced during DDR by ATM and p53 upregulation of p21 [84].

2.5 Other DDR pathways

ATM and ATR also integrate into DDR several other pathways that are essential to provide an adequate and proportionate response to all kind of injuries. For instance, no proper DDR can occur without the upregulation of dNTP for DNA repair [85]. This upregulation requires tight control, as excessive dNTP production can lead to increased mutation frequency [86]. In the presence of DNA damage, DDR kinases regulate RNR—the kinase that catalyzes rate-limiting step during dNTP production—at multiple levels. For instance, p53 regulates the expression levels of RNR; whereas, ATM phosphorylation increases the stability of RNR [87]. In addition, ATR signaling inhibits degradation of some RNR subunits, further contributing to the regulation of dNTP levels by DDR kinases.

Dysfunctional telomeres can also activate ATM and ATR and elicit a response that includes halting the cell cycle and induction of senescence [88]. Telomere dysfunction can arise when errors in the Shelterin complex render telomeres unprotected. Loss of protection at telomeres can also occur by the natural attrition of telomere length experienced during DNA replication in cells that do not express telomerase [89]. In both cases, DNA ends at telomeres can be mistakenly recognized as DNA damage events and activate DDR.

Recently, activation of autophagy has emerged as another tool that DDR can use to fight severe DNA damage. While autophagy was initially thought to be exclusively activated in response to cellular damage or starvation, there is clear evidence that DNA damage can also trigger autophagy [90]. For instance, the action of mTOR—the main autophagy inhibitor—can be repressed either in an ATM or PARP1 dependent manner following DNA damage, effectively promoting autophagy [7]. Consistent with this, in response to ROS mediated damage, ATM can induce selective degradation of mitochondria by autophagy (also known as

mitophagy) and pexophagy—the autophagic degradation of peroxisomes [91–93]. Integration of autophagy pathways as part of DDR repertoire may allow cells in stress to attempt pro-survival pathways first before succumbing to apoptosis.

While the complex relationships between DDR and inflammation are beginning to emerge, it is clear that ROS and other types of genomic injuries can elicit a pro-inflammatory response. As part of DDR, this pro-survival cell response is mediated mostly through ATM and PARP1 [94]. ATM directly binds and phosphorylates IKK-γ (NEMO), the regulatory subunit of the IKK complex that activates NF-kB [41]. Along with PARP1-mediated post-translational modifications, ATM phosphorylation of IKK-γ promotes activation of IKK and subsequent activation of NF-kB [41, 95–97]. Therefore, this critical pro-inflammatory enzyme is under DDR control, where it can function as a transcription factor promoting expression of pro-inflammatory cytokines and DNA repair genes [76, 94, 95, 98]. In addition, ATM is involved in a pro-inflammatory pathway known as senescence-associated secretory phenotype (SASP), a complex mechanism that secretes, among others, pro-inflammatory cytokines [94, 99].

3. Molecular basis for ataxia telangiectasia syndrome

A-T is an autosomal recessive genetic disease that affects 1 in every 40,000–100,00 births with an estimated 0.5–1% of the global population being carriers of the illness [100]. Patients confront a variety of clinical manifestations throughout their lives, with the inability to control body movements, or ataxia, being one the earliest to appear [101]. The underlying cause for the ataxia is progressive neurodegeneration, particularly of the cerebellum, which also induces dysarthria (speech difficulties), poor balance, and uncontrolled eye movements. Neurodegeneration involves the gradual disappearance of Purkinje, granular cells and the molecular layer of the cerebellar cortex, and expands to the brain stem and the spinal cord. A-T is also characterized by the presence of vascular abnormalities (telangiectasia) that manifest as red spider-like veins, present mostly in the eyes, but also found in cheeks, ears, neck, and other parts of patients' bodies [102, 103].

In addition to the ataxia and telangiectasia, A-T patients can suffer from a plethora of other clinical symptoms. They have a higher incidence of cancer, diabetes, and show premature aging. They manifest radiosensitivity, sterility, and immunodeficiencies with an elevated risk of developing autoimmune diseases such as arthritis, vitiligo, or immune thrombocytopenia [104]. Authors have also suggested that A-T patients may suffer from prolonged chronic inflammation [94]. Consistent with this, high levels of pro-inflammation cytokines are present in their serum even in the absence of infections [51, 52].

While mutations in other DDR gene can induce similar symptomatology, defective or absent, ATM is the sole genetic cause of A-T. Hundreds of pathogenic mutations have been identified in ATM from A-T patients, many of them altering splicing or causing frameshifts that result in premature termination codons. As a result, ATM is often either missing or containing truncations of different extents in A-T cells. Clinical manifestations correlate with the severity of the mutation, with milder forms of the syndrome appearing in individuals bearing mutations with mild effects on ATM function and vice versa [105].

3.1 Neurodegeneration

The most apparent clinical manifestation of the disease is probably also the most problematic to explain at the molecular level. The question of why mutations in a gene involved in DDR would have specific and discriminating effects in the neural

system remains to be fully answered [5, 106]. One of the problems in answering this question is that mouse models lacking functional ATM reconstitute most of the pleiotropic effects of A-T, except for neurodegeneration [107–109].

It is clear that during neurodevelopment, rapidly dividing cells—with high energetic demands and increased mitochondria respiration—face increasing levels of threats to the integrity of their genome [110, 111]. High metabolic rates increase ROS, and produce oxidative stress, which combined with the high demand for transcription, may render these cells more susceptible to faulty DNA repair mechanisms [110, 112]. This view is consistent with the high prevalence of neurological problems in patients bearing mutations in DNA repair genes [5, 9]. Authors have proposed a model where different stages during neurodevelopment are more susceptible to mutations in different DNA repair pathways, with HR having major roles during phases of rapid proliferation—when a sister chromatid is readily available—and NHEJ being required during late development when cells undergo differentiation in G1/G0 [9]. This would explain why mutations in HR often result in embryonic lethality; whereas, mutations in some NHEJ genes present neurodevelopment problems such as microcephalia. In this model, single strand lesion repair would be required for post-developmental maintenance of neural tissue.

Cerebellum neurodegeneration in A-T patients also establishes ATM as a requirement to maintain neural tissue. The accumulation of unrepaired lesions during development—and beyond—results in degeneration problems later [113]. This is likely to happen at any tissue, but it would affect the neural system in particular, and with greater virulence, due to the longevity of its cells and the subsequent longer exposure to mutagenic agents. This injury build-up would occur progressively, mimicking the progressive nature of neurodegeneration in A-T patients.

Supporting this view, there are clear indications that neural A-T cells are under genotoxic stress. Mice cells lacking ATM gradually accumulate DSBs and show depleted levels of oxidized and reduced forms of NAD in cerebellar tissue, a hallmark of cells undergoing high levels of oxidative stress [114]. Interestingly, depletion of NAD levels only occurs in cerebellar tissues, but not in other parts of the brain, indicating that oxidative stress may be particularly acute in the cerebellum. These data are consistent with other studies that found high levels of oxidative stress in the cerebellum and Purkinje cells in particular, which likely explains the higher prevalence of neurodegeneration in the cerebellum than in other parts of the neural system [115]. The reason for the localized high levels of oxidative stress in cerebellar tissue compared to other regions of the neural system is not known, nor is the reason for the lack of a cerebellar degeneration phenotype in mice lacking ATM despite increased levels of oxidative damage.

These studies strongly suggest that the inability to repair damage caused by oxidative stress is the more plausible cause of cerebellar neurodegeneration in A-T and thus, the roles of ATM during the repair of single strand lesions may provide the molecular basis for the disease. The correlation between impaired single strand lesions repair and failure of neural tissue maintenance was further corroborated in mice that showed extensive neuron loss in the cerebellum when XRCC1 expression was selectively prevented in their brain [116]. While ATM mostly acts in DSB repair, it can also play roles during single strand lesion repair. As mentioned before, SSBs can activate ATM and promote BER by the ATM-mediated phosphorylation of XRCC1 (see Section 2.1) [46]. Whether or not, impairment of this DDR branch is related to the neurodegeneration observed in A-T remains to be elucidated.

Authors have also proposed that neurological problems arising in A-T patients may be related to the faulty resolution of R-loops in locations where active transcription is halted due to the presence of DNA lesions [9, 13]. R-loops are hybrids formed by two strands of DNA and one of RNA that are generated in a variety of circumstances and locations and are known to pose a risk to genome stability

[117]. Paused RNA polymerase sites activate ATM, which then elicit a response that includes interactions with spliceosome components that may mediate R-loop resolution [118]. In the cerebellum, the combination of high levels of oxidative stress with high demands of transcription may produce an abnormally high amount of paused transcription sites due to DNA damage. In the absence of ATM, R-loops may not be adequately resolved, eventually creating a scenario incompatible with cell life.

3.2 Telangiectasia

The localized abnormal vascular formations that A-T patients show in several parts of their bodies—particularly in the eyes—is one of the most obvious and yet least investigated phenotypes of the disease [119]. Telangiectasia is highly prevalent in A-T, only missing in patients bearing mild ATM mutations that maintain some residual protein function [120]. Very little is known about the molecular mechanism that prompts telangiectasia when ATM is absent or dysfunctional. The current model proposes that oxidative stress caused by a lack of functional ATM may upregulate HIF1A levels, a hypoxia-activated transcription factor that can induce vascularization by increasing the levels of angiogenesis factor VEGF [120]. Intriguingly, SAPS also induces secretion of VEGF, suggesting a link between this DDR controlled pathway and vascularization [121, 122].

3.3 Immunodeficiency and inflammation

A-T patients can show low levels of at least one type of immunoglobulin, inadequate antibody responses to infections and abnormal T and B lymphocyte counts [123, 124]. These phenotypes can be attributed to the roles that ATM has in regulating NHEJ during V(D)J recombination and class-switch recombination (CSR), two recombination processes required to produce antibody diversity during adaptive immunity. Both V(D)J and CSR involve induction of programmed DSBs followed by ATM-aided NHEJ repair [125]. For instance, during V(D)J ATM localizes to break sites and regulate NHEJ components, while p53BP1 phosphorylation by ATM is a crucial event during CSR. The regulatory roles that ATM exerts on these two processes are likely to be extensive and involve other DDR pathways. In A-T patients with immunodeficiencies, programmed DSBs remain unrepaired, and their persistence can cause severe T and B-cell developmental problems [126–128].

There is growing evidence that the innate immune response may be tightly linked to several clinical manifestations observed in A-T patients. Lack of ATM creates high levels of ROS and oxidative damage, which is known to induce pro-inflammatory cytokines [111, 129, 130]. ATM-deficient cells cannot trigger pexophagy and other forms of autophagy to counteract the negatives effect of oxidative damage, further compounding the problem [91]. Persistent genotoxic stress can, therefore, create chronic inflammation in A-T patients, a condition linked to several A-T symptoms: increased levels of cardiovascular and autoimmune diseases, insulin resistance, and aging. Tellingly, the immune response contributes to neurodegeneration during Alzheimer's disease, possibly suggesting that in A-T patients, chronic inflammation may also contribute to neurodegeneration in cerebellar tissues suffering high levels of genotoxic stress [131].

3.4 Radiosensitivity and increased cancer risk

Several DDR pathways contribute to the increased cancer risk seen in A-T patients. The inability of A-T cells to coordinate DNA repair with other DDR pathways can leave unrepaired genomic injuries and elevate the number of mutations in cells—including perilous DSBs—rendering cells highly sensitive to ionizing

radiation. Lack of ATM permits these mutations to escape cell cycle checkpoints control and be transmitted to daughter cells, further contributing to tumorigenesis. This process can continue unchecked, as the genomic instability that it produces does not trigger apoptosis when ATM is absent or dysfunctional.

One of the most common malignancies in A-T patients is breast cancer [132]. Even heterozygous individuals bearing debilitating mutations in just one of the ATM genes also have increased breast cancer incidence. While many DDR components are likely to participate in breast cancer tumorigenesis, the loss of the direct control that ATM exerts over BRAC1 is likely one of the major contributing factors. Lymphomas of B-cell origin and leukemia of T-cell origin are also very common in A-T patients, as unrepaired programmed DSBs persisting in developing T and B cells can often be the substrate of translocations [133].

3.5 Other clinical features

Both male and female A-T patients show infertility due to abnormal meiosis progression. During meiosis, ATM controls the number of DSBs created by SPO11 and ensures their even distribution in the genome [134]. This is achieved by recruiting ATM to SPO11-generated DSBs, which inhibits the formation of further cuts in the vicinity of break sites. Mice models have shown a meiotic arrest in prophase I, faulty synapsis, and chromosome fragmentation leading to massive germ cell loss [107, 135], suggesting that the loss of ATM's roles during meiosis is the underlying cause of infertility in A-T patients.

A-T patients can suffer from insulin resistance and thus, have a higher risk of developing diabetes, a clinical feature that they share with carriers of the disease. The cause for this phenotype is likely to be multifactorial, but it is well-defined that ATM phosphorylates several targets—e.g., translation regulation 4E-BP1—in response to insulin [25]. Furthermore, a lack of fully functional ATM correlates with an inhibition of IRS1 (insulin receptor substrate 1) and low levels of IGF1-R (insulin-like growth factor1 receptor), suggesting possible mechanisms causing this clinical feature [94, 136, 137].

4. Conclusion

While much progress has been made to understand A-T at the molecular level, there are still important questions that remain unanswered. This is especially true for the cerebellar neurodegeneration observed in A-T patients, where unknown tissue-specific factors may be at play. The genesis and the extent of some of the A-T clinical features are likely to be the result of interwoven relationships between many pathways and pathologies described in here and hence, elucidating their connections will be crucial to fully understand the disease and develop effective tools for its treatment.

Acknowledgements

This manuscript was funded and supported by the Smith Chair in Biology at the University of St. Thomas.

Conflict of interest

I have no conflict of interest to declare.

IntechOpen

Author details

Albert Ribes-Zamora
Biology Department, University of St. Thomas, Houston, USA

*Address all correspondence to: ribesza@stthom.edu

IntechOpen

References

[1] Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009

[2] Sancar A, Lindsey-Boltz LA, Ünsal-Kaçmaz K, Linn S. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annual Review of Biochemistry. 2004

[3] Sirbu BM, Cortez D. DNA damage response: Three levels of DNA repair regulation. Cold Spring Harbor Perspectives in Biology. 2013

[4] Ciccia A, Elledge SJ. The DNA damage response: Making it safe to play with knives. Molecular Cell. 2010

[5] Coon EA, Benarroch EE. DNA damage response selected review and neurologic implications. Neurology. 2018

[6] Harper JW, Elledge SJ. The DNA damage response: Ten years after. Molecular Cell. 2007

[7] Cartwright BM, Musich PR, Zou Y. DNA damage: Cellular responses, repair and cancer treatment. In: Regulation of Signal Transduction in Human Cell. Singapore: Springer Nature; 2018. pp. 99-127

[8] Shibata A, Jeggo PA. DNA double-strand break repair in a cellular context. Clinical Oncology. 2014

[9] Rulten SL, Caldecott KW. DNA strand break repair and neurodegeneration. DNA Repair (Amst). 2013

[10] Enriquez-Rios V, Dumitrache LC, Downing SM, Li Y, Brown EJ, Russell HR, et al. DNA-PKcs, ATM, and ATR interplay maintains genome integrity during neurogenesis. The Journal of Neuroscience. 2017

[11] Stracker TH, Roig I, Knobel PA, Marjanović M. The ATM signaling network in development and disease. Frontiers in Genetics. 2013

[12] Kulkarni A, Wilson DM. The involvement of DNA-damage and -repair defects in neurological dysfunction. American Journal of Human Genetics. 2008

[13] Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: The trinity at the heart of the DNA damage response. Molecular Cell. 2017

[14] Rass U, Ahel I, West SC. Defective DNA repair and neurodegenerative disease. Cell. 2007

[15] Antoccia A, Kobayashi J, Tauchi H, Matsuura S, Komatsu K. Nijmegen breakage syndrome and functions of the responsible protein, NBS1. Genome Dynamics. 2006

[16] O'Driscoll M, Ruiz-Perez VL, Woods CG, Jeggo PA, Goodship JA. A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein [ATR] results in Seckel syndrome. Nature Genetics. 2003

[17] Zhou Y, Lee JH, Jiang W, Crowe JL, Zha S, Paull TT. Regulation of the DNA damage response by DNA-PKcs inhibitory phosphorylation of ATM. Molecular Cell. 2017

[18] Kozlov SV, Graham ME, Jakob B, Tobias F, Kijas AW, Tanuji M, et al. Autophosphorylation and ATM activation: Additional sites add to the complexity. The Journal of Biological Chemistry. 2011

[19] Bakkenist CJ, Kastan MB. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature. 2003

[20] Lavin MF, Kozlov S. ATM activation and DNA damage response. Cell Cycle. 2007

[21] Bannister AJ, Gottlieb TM, Kouzarides T, Jackson SP. c-Jun is phosphorylated by the DNA-dependent protein kinase in vitro; definition of the minimal kinase recognition motif. Nucleic Acids Research. 1993

[22] Traven A, Heierhorst J. SQ/TQ cluster domains: Concentrated ATM/ATR kinase phosphorylation site regions in DNA-damage-response proteins. BioEssays. 2005

[23] Cheung HC, San Lucas FA, Hicks S, Chang K, Bertuch AA, Ribes-Zamora A. An S/T-Q cluster domain census unveils new putative targets under Tel1/Mec1 control. BMC Genomics. 2012

[24] Cara L, Baitemirova M, Follis J, Larios-Sanz M, Ribes-Zamora A. The ATM- and ATR-related SCD domain is over-represented in proteins involved in nervous system development. Scientific Reports. 2016

[25] Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER, Hurov KE, Luo J, et al. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science. 2007

[26] Matsuoka S, Rotman G, Ogawa A, Shiloh Y, Tamai K, Elledge SJ. Ataxia telangiectasia-mutated phosphorylates Chk2 in vivo and in vitro. Proceedings of the National Academy of Sciences. 2000

[27] Matsuoka S, Huang M, Elledge SJ. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. Science. 1998

[28] Banin S, Moyal L, Shieh SY, Taya Y, Anderson CW, Chessa L, et al. Enhanced phosphorylation of p53 by ATM in response to DNA damage. Science. 1998

[29] Guo Z, Kozlov S, Lavin MF, Person MD, Paull TT. ATM activation by oxidative stress. Science. 2010

[30] Ray Chaudhuri A, Nussenzweig A. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nature Reviews. Molecular Cell Biology. 2017

[31] Wei H, Yu X. Functions of PARylation in DNA damage repair pathways. Genomics, Proteomics & Bioinformatics. 2016

[32] Williams GJ, Lees-Miller SP, Tainer JA. Mre11-Rad50-Nbs1 conformations and the control of sensing, signaling, and effector responses at DNA double-strand breaks. DNA Repair. 2010

[33] Wang H, Shi LZ, Wong CCL, Han X, Hwang PYH, Truong LN, et al. The interaction of CtIP and Nbs1 connects CDK and ATM to regulate HR-mediated double-strand break repair. PLoS Genetics. 2013

[34] Rogakou EP, Pilch DR, Orr AH, Ivanova VS, Bonner WM. DNA double-stranded breaks induce histone H2AX phosphorylation on serine 139. The Journal of Biological Chemistry. 1998

[35] Stucki M, Clapperton JA, Mohammad D, Yaffe MB, Smerdon SJ, Jackson SP. MDC1 directly binds phosphorylated histone H2AX to regulate cellular responses to DNA double-strand breaks. Cell. 2005

[36] Jungmichel S, Clapperton JA, Lloyd J, Hari FJ, Spycher C, Pavic L, et al. The molecular basis of ATM-dependent dimerization of the Mdc1 DNA damage checkpoint mediator. Nucleic Acids Research. 2012

[37] Adams KE, Medhurst AL, Dart DA, Lakin ND. Recruitment of ATR to sites of ionising radiation-induced DNA damage requires ATM and components of the MRN protein complex. Oncogene. 2006

[38] Shibata A, Conrad S, Birraux J, Geuting V, Barton O, Ismail A, et al. Factors determining DNA double-strand break repair pathway choice in G2 phase. The EMBO Journal. 2011

[39] Chapman JR, Taylor MRG, Boulton SJ. Playing the end game: DNA double-Strand break repair pathway choice. Molecular Cell. 2012

[40] Xu B, O'Donnell AH, Kim ST, Kastan MB. Phosphorylation of serine 1387 in Brca1 is specifically required for the ATM-mediated S-phase checkpoint after ionizing irradiation. Cancer Research. 2002

[41] Wu ZH, Shi Y, Tibbetts RS, Miyamoto S. Molecular linkage between the kinase ATM and NF-κB signaling in response to genotoxic stimuli. Science. 2006

[42] Sartori AA, Lukas C, Coates J, Mistrik M, Fu S, Bartek J, et al. Human CtIP promotes DNA end resection. Nature. 2007

[43] Jowsey PA, Doherty AJ, Rouse J. Human PTIP facilitates ATM-mediated activation of p53 and promotes cellular resistance to ionizing radiation. The Journal of Biological Chemistry. 2004

[44] Hustedt N, Durocher D. The control of DNA repair by the cell cycle. Nature Cell Biology. 2017

[45] Jiang W, Crowe JL, Liu X, Nakajima S, Wang Y, Li C, et al. Differential phosphorylation of DNA-PKcs regulates the interplay between end-processing and end-ligation during nonhomologous end-joining. Molecular Cell. 2015

[46] Chou WC, Hu LY, Hsiung CN, Shen CY. Initiation of the ATM-Chk2 DNA damage response through the base excision repair pathway. Carcinogenesis. 2015

[47] Wilson DM, Bohr VA. The mechanics of base excision repair, and its relationship to aging and disease. DNA Repair (Amst). 2007

[48] Wu X, Shell SM, Yang Z, Zou Y. Phosphorylation of nucleotide excision repair factor xeroderma pigmentosum group A by ataxia telangiectasia mutated and Rad3-related-dependent checkpoint pathway promotes cell survival in response to UV irradiation. Cancer Research. 2006

[49] Shell SM, Li Z, Shkriabai N, Kvaratskhelia M, Brossey C, Serrano MA, et al. Checkpoint kinase ATR promotes nucleotide excision repair of UV-induced DNA damage via physical interaction withxeroderma pigmentosum group a. The Journal of Biological Chemistry. 2009

[50] Barckhausen C, Roos WP, Naumann SC, Kaina B. Malignant melanoma cells acquire resistance to DNA interstrand cross-linking chemotherapeutics by p53-triggered upregulation of DDB2/XPC-mediated DNA repair. Oncogene. 2014

[51] Wang XW, Yeh H, Schaeffer L, Roy R, Moncollin V, Egly JM, et al. p53 modulation of TFIIH-associated nucleotide excision repair activity. Nature Genetics. 1995

[52] Wang QE, Zhu Q, Wani MA, Wani G, Chen J, Wani AA. Tumor suppressor p53 dependent recruitment of nucleotide excision repair factors XPC and TFIIH to DNA damage. DNA Repair (Amst). 2003

[53] Singh TR, Ali AM, Paramasivam M, Pradhan A, Wahengbam K, Seidman MM, et al. ATR-dependent phosphorylation of FANCM at serine 1045 is essential for FANCM functions. Cancer Research. 2013

[54] Collins NB, Wilson JB, Bush T, Thomashevski A, Roberts KJ, Jones NJ,

et al. ATR-dependent phosphorylation of FANCA on serine 1449 after DNA damage is important for FA pathway function. Blood. 2009

[55] Ceccaldi R, Sarangi P, D'Andrea AD. The Fanconi anaemia pathway: New players and new functions. Nature Reviews. Molecular Cell Biology. 2016

[56] Offer H, Zurer I, Banfalvi G, Reha'K M, Falcovitz A, Milyavsky M, et al. p53 modulates base excision repair activity in a cell cycle-specific manner after genotoxic stress. Cancer Research. 2001

[57] Zurer I, Hofseth LJ, Cohen Y, Xu-Welliver M, Hussain SP, Harris CC, et al. The role of p53 in base excision repair following genotoxic stress. Carcinogenesis. 2004

[58] Romanova LY, Willers H, Blagosklonny MV, Powell SN. The interaction of p53 with replication protein a mediates suppression of homologous recombination. Oncogene. 2004

[59] Ammazzalorso F, Pirzio LM, Bignami M, Franchitto A, Pichierri P. ATR and ATM differently regulate WRN to prevent DSBs at stalled replication forks and promote replication fork recovery. The EMBO Journal. 2010

[60] Croteau DL, Popuri V, Opresko PL, Bohr VA. Human RecQ helicases in DNA repair, recombination, and replication. Annual Review of Biochemistry. 2014

[61] Liu M, Hu WX. Cell cycle checkpoint signaling through the ATR and ATM kinases. In: 2nd International Conference on Information Science and Engineering, ICISE2010 – Proceedings; 2010

[62] Bartek J, Lukas J. Mammalian G1- and S-phase checkpoints in response to DNA damage. Current Opinion in Cell Biology. 2001

[63] Xiao Z, Chen Z, Gunasekera AH, Sowin TJ, Rosenberg SH, Fesik S, et al. Chk1 mediates S and G2 arrests through Cdc25A degradation in response to DNA-damaging agents. The Journal of Biological Chemistry. 2003

[64] Mailand N, Falck J, Lukas C, Syljuåsen RG, Welcker M, Bartek J, et al. Rapid destruction of human Cdc25A in response to DNA damage. Science. 2000

[65] Abbas T, Dutta A. P21 in cancer: Intricate networks and multiple activities. Nature Reviews. Cancer. 2009

[66] Bartek J, Lukas J. Chk1 and Chk2 kinases in checkpoint control and cancer. Cancer Cell. 2003

[67] Liu S, Shiotani B, Lahiri M, Maréchal A, Tse A, Leung CCY, et al. ATR autophosphorylation as a molecular switch for checkpoint activation. Molecular Cell. 2011

[68] Sanchez Y, Bachant J, Wang H, Hu F, Liu D, Tetzlaff M, et al. Control of the DNA damage checkpoint by Chk1 and Rad53 protein kinases through distinct mechanisms. Science. 1999

[69] Sanchez Y, Wong C, Thoma RS, Richman R, Wu Z, Piwnica-Worms H, et al. Conservation of the Chk1 checkpoint pathway in mammals: Linkage of DNA damage to Cdk regulation through Cdc25. Science. 1997

[70] Peng CY, Graves PR, Thoma RS, Wu Z, Shaw AS, Piwnica-Worms H. Mitotic and G2 checkpoint control: Regulation of 14-3-3 protein binding by phosphorylation of Cdc25c on serine-216. Science. 1997

[71] Lee J, Kumagai A, Dunphy WG. Positive regulation of Wee1 by Chk1 and 14-3-3 proteins. Molecular Biology of the Cell. 2001

[72] Yang Q, Manicone A, Coursen JD, Linke SP, Nagashima M, Forgues M,

et al. Identification of a functional domain in a GADD45-mediated G2/M checkpoint. The Journal of Biological Chemistry. 2000

[73] Harvey SL, Charlet A, Haas W, Gygi SP, Kellogg DR. Cdk1-dependent regulation of the mitotic inhibitor Wee1. Cell. 2005

[74] Zitouni S, Nabais C, Jana SC, Guerrero A, Bettencourt-Dias M. Polo-like kinases: Structural variations lead to multiple functions. Nature Reviews. Molecular Cell Biology. 2014

[75] Mackay DR, Ullman KS. ATR and a Chk1-Aurora B pathway coordinate postmitotic genome surveillance with cytokinetic abscission. Molecular Biology of the Cell. 2015

[76] Christmann M, Kaina B. Transcriptional regulation of human DNA repair genes following genotoxic stress: Trigger mechanisms, inducible responses and genotoxic adaptation. Nucleic Acids Research. 2013

[77] Adimoolam S, Ford JM. p53 and DNA damage-inducible expression of the xeroderma pigmentosum group C gene. Proceedings of the National Academy of Sciences. 2002

[78] Jenkins LMM, Durell SR, Mazur SJ, Appella E. p53 N-terminal phosphorylation: A defining layer of complex regulation. Carcinogenesis. 2012

[79] Gannon HS, Woda BA, Jones SN. ATM phosphorylation of Mdm2 Ser394 regulates the amplitude and duration of the DNA damage response in mice. Cancer Cell. 2012

[80] Vousden KH, Lane DP. p53 in health and disease. Nature Reviews. Molecular Cell Biology. 2007

[81] Nakano K, Vousden KH. PUMA, a novel proapoptotic gene, is induced by p53. Molecular Cell. 2001

[82] Wu Y, Mehew JW, Heckman CA, Arcinas M, Boxer LM. Negative regulation of bcl-2 expression by p53 in hematopoietic cells. Oncogene. 2001

[83] Shimizu I, Yoshida Y, Suda M, Minamino T. DNA damage response and metabolic disease. Cell Metabolism. 2014

[84] Jackson JG, Pereira-Smith OM. p53 is preferentially recruited to the promoters of growth arrest genes p21 and GADD45 during replicative senescence of normal human fibroblasts. Cancer Research. 2006

[85] Elledge SJ, Zhou Z, Allen JB, Navas TA. DNA damage and cell cycle regulation of ribonucleotide reductase. BioEssays. 1993

[86] Chabes A, Georgieva B, Domkin V, Zhao X, Rothstein R, Thelander L. Survival of DNA damage in yeast directly depends on increased dNTP levels allowed by relaxed feedback inhibition of ribonucleotide reductase. Cell. 2003

[87] Tanaka H, Arakawa H, Yamaguchi T, Shiraishi K, Fukuda S, Matsui K, et al. A ribonucleotide reductase gene involved in a p53-dependent cell-cycle checkpoint for DNA damage. Nature. 2000

[88] de Lange T. Shelterin-mediated telomere protection. Annual Review of Genetics. 2018

[89] Reaper PM, Clay-Farrace L, Fiegler H, Carr P, Von Zglinicki T, Saretzki G, et al. A DNA damage checkpoint response in telomere-initiated senescence. Nature. 2003

[90] Abedin MJ, Wang D, McDonnell MA, Lehmann U, Kelekar A. Autophagy delays apoptotic death in breast cancer cells following DNA damage. Cell Death and Differentiation. 2007

[91] Zhang J, Tripathi DN, Jing J, Alexander A, Kim J, Powell RT, et al.

ATM functions at the peroxisome to induce pexophagy in response to ROS. Nature Cell Biology. 2015

[92] Valentin-Vega YA, Kastan MB. A new role for ATM: Regulating mitochondrial function and mitophagy. Autophagy. 2012

[93] Valentin-Vega YA, MacLean KH, Tait-Mulder J, Milasta S, Steeves M, Dorsey FC, et al. Mitochondrial dysfunction in ataxia-telangiectasia. Blood. 2012

[94] Zaki-Dizaji M, Akrami SM, Azizi G, Abolhassani H, Aghamohammadi A. Inflammation, a significant player of ataxia–telangiectasia pathogenesis? Inflammation Research. 2018

[95] Hellweg CE. The nuclear factor κB pathway: A link to the immune system in the radiation response. Cancer Letters. 2015

[96] Hadian K, Krappmann D, Hayden MS, Ghosh S, Vallabhapurapu S, Karin M, et al. Signals from the nucleus: Activation of NF-kappaB by cytosolic ATM in the DNA damage response. Science Signaling. 2011

[97] Stilmann M, Hinz M, Arslan SÇ, Zimmer A, Schreiber V, Scheidereit C. A nuclear poly[ADP-ribose]-dependent signalosome confers DNA damage-induced IκB kinase activation. Molecular Cell. 2009

[98] Miyamoto S. Nuclear initiated NF-κB signaling: NEMO and ATM take center stage. Cell Research. 2011

[99] Kang C, Xu Q, Martin TD, Li MZ, Demaria M, Aron L, et al. The DNA damage response induces inflammation and senescence by inhibiting autophagy of GATA4. Science. 2015

[100] Zaki-Dizaji M, Akrami SM, Abolhassani H, Rezaei N, Aghamohammadi A. Ataxia telangiectasia syndrome: Moonlighting ATM. Expert Review of Clinical Immunology. 2017

[101] Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. DNA Repair. 2004

[102] Verhagen MMM, Abdo WF, Willemsen MAAP, Hogervorst FBL, Smeets DFCM, Hiel JAP, et al. Clinical spectrum of ataxia-telangiectasia in adulthood. Neurology. 2009

[103] Taylor AMR, Harnden DG, Arlett CF, Harcourt SA, Lehmann AR, Stevens S, et al. Ataxia telangiectasia: A human mutation with abnormal radiation sensitivity. Nature. 1975

[104] Ammann AJ, Hong R. Autoimmune phenomena in ataxia telangiectasia. The Journal of Pediatrics. 1971

[105] Verhagen MMM, Last JI, Hogervorst FBL, Smeets DFCM, Roeleveld N, Verheijen F, et al. Presence of ATM protein and residual kinase activity correlates with the phenotype in ataxia-telangiectasia: A genotype-phenotype study. Human Mutation. 2012

[106] Biton S, Barzilai A, Shiloh Y. The neurological phenotype of ataxia-telangiectasia: Solving a persistent puzzle. DNA Repair (Amst). 2008

[107] Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, et al. Atm-deficient mice: A paradigm of ataxia telangiectasia. Cell. 1996

[108] Elson A, Wang Y, Daugherty CJ, Morton CC, Zhou F, Campos-Torres J, et al. Pleiotropic defects in ataxia-telangiectasia protein-deficient mice. Proceedings of the National Academy of Sciences. 1996

[109] Xu Y, Ashley T, Brainerd EE, Bronson RT, Meyn MS, Baltimore D. Targeted disruption of ATM leads to growth retardation, chromosomal

fragmentation during meiosis, immune defects, and thymic lymphoma. Genes & Development. 1996

[110] Barlow C, Dennery PA, Shigenaga MK, Smith MA, Morrow JD, Roberts LJ, et al. Loss of the ataxia–telangiectasia gene product causes oxidative damage in target organs. Neurobiology. 1999

[111] Kamsler A, Daily D, Hochman A, Stern N, Shiloh Y, Rotman G, et al. Increased oxidative stress in ataxia telangiectasia evidenced by alterations in redox state of brains from ATM-deficient mice. Cancer Research. 2001

[112] Weissman L, de Souza-Pinto NC, Stevnsner T, Bohr VA. DNA repair, mitochondria, and neurodegeneration. Neuroscience. 2007

[113] Rutten BPF, Schmitz C, Gerlach OHH, Oyen HM, de Mesquita EB, Steinbusch HWM, et al. The aging brain: Accumulation of dna damage or neuron loss? Neurobiology of Aging. 2007

[114] Stern N, Hochman A, Zemach N, Weizman N, Hammel I, Shiloh Y, et al. Accumulation of DNA damage and reduced levels of nicotine adenine dinucleotide in the brains of ATM-deficient mice. The Journal of Biological Chemistry. 2002

[115] Yang Y, Hui CW, Li J, Herrup K. The interaction of the ATM genotype with inflammation and oxidative stress. PLoS One. 2014

[116] Lee Y, Katyal S, Li Y, El-Khamisy SF, Russell HR, Caldecott KW, et al. The genesis of cerebellar interneurons and the prevention of neural DNA damage require XRCC1. Nature Neuroscience. 2009

[117] Aguilera A, García-Muse T. R loops: From transcription byproducts to threats to genome stability. Molecular Cell. 2012

[118] Tresini M, Warmerdam DO, Kolovos P, Snijder L, Vrouwe MG, Demmers JAA, et al. The core spliceosome as target and effector of non-canonical ATM signalling. Nature. 2015

[119] Kamiya M, Yamanouchi H, Yoshida T, Arai H, Yokoo H, Sasaki A, et al. Ataxia telangiectasia with vascular abnormalities in the brain parenchyma: Report of an autopsy case and literature review. Pathology International. 2001

[120] Schoenaker MHD, Van Os NJH, Van der Flier M, Van Deuren M, Seyger MM, Taylor AMR, et al. Telangiectasias in ataxia telangiectasia: Clinical significance, role of ATM deficiency and potential pathophysiological mechanisms. European Journal of Medical Genetics. 2018

[121] Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, van Doorn R, Desmet CJ, et al. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. Cell. 2008

[122] Acosta JC, O'Loghlen A, Banito A, Guijarro MV, Augert A, Raguz S, et al. Chemokine signaling via the CXCR2 receptor reinforces senescence. Cell. 2008

[123] Driessen GJ, Ijspeert H, Weemaes CMR, Haraldsson Á, Trip M, Warris A, et al. Antibody deficiency in patients with ataxia telangiectasia is caused by disturbed B- and T-cell homeostasis and reduced immune repertoire diversity. The Journal of Allergy and Clinical Immunology. 2013

[124] Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM. Immunodeficiency and infections in ataxia-telangiectasia. Journal of Pediatrics. 2004

[125] Bassing CH, Swat W, Alt FW. The mechanism and regulation of

chromosomal V[D]J recombination. Cell. 2002

[126] Ghiasy S, Parvaneh L, Azizi G, Sadri G, Zaki dizaji M, Abolhassani H, et al. The clinical significance of complete class switching defect in Ataxia telangiectasia patients. Expert Review of Clinical Immunology. 2017

[127] Kraus M, Lev A, Simon AJ, Levran I, Nissenkorn A, Levi YB, et al. Disturbed B and T cell homeostasis and neogenesis in patients with ataxia telangiectasia. Journal of Clinical Immunology. 2014

[128] Bredemeyer AL, Huang C-Y, Walker LM, Bassing CH, Sleckman BP. Aberrant V[D]J recombination in ataxia telangiectasia mutated-deficient lymphocytes is dependent on nonhomologous DNA end joining. Journal of Immunology. 2008

[129] Rodier F, Coppé JP, Patil CK, Hoeijmakers WAM, Muñoz DP, Raza SR, et al. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nature Cell Biology. 2009

[130] Rodier F, Munoz DP, Teachenor R, Chu V, Le O, Bhaumik D, et al. DNA-SCARS: Distinct nuclear structures that sustain damage-induced senescence growth arrest and inflammatory cytokine secretion. Journal of Cell Science. 2011

[131] Fakhoury M. Role of immunity and inflammation in the pathophysiology of neurodegenerative diseases. Neurodegenerative Diseases. 2015

[132] Estiar MA, Mehdipour P. ATM in breast and brain tumors: A comprehensive review. Cancer Biology & Medicine. 2018

[133] Nussenzweig A, Nussenzweig MC. Origin of chromosomal translocations in lymphoid cancer. Cell. 2010

[134] Lange J, Pan J, Cole F, Thelen MP, Jasin M, Keeney S. ATM controls meiotic double-strand-break formation. Nature. 2011

[135] Hamer G, Kal HB, Westphal CH, Ashley T, de Rooij DG. Ataxia telangiectasia mutated expression and activation in the Testis1. Biology of Reproduction. 2004

[136] Macaulay VM, Salisbury AJ, Bohula EA, Playford MP, Smorodinsky NI, Shiloh Y. Downregulation of the type 1 insulin-like growth factor receptor in mouse melanoma cells is associated with enhanced radiosensitivity and impaired activation of ATM kinase. Oncogene. 2001

[137] Ching JK, Luebbert SH, Collins RL IV, Zhang Z, Marupudi N, Banerjee S, et al. Ataxia telangiectasia mutated impacts insulin-like growth factor 1 signalling in skeletal muscle. Experimental Physiology. 2013