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Review

The hallmarks of aging in Ataxia-Telangiectasia

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ABSTRACT

Ataxia-telangiectasia (A-T) is caused by absence of the catalytic activity of ATM, a protein kinase that plays a central role in the DNA damage response, many branches of cellular metabolism, redox and mitochondrial homeostasis, and cell cycle regulation. A-T is a complex disorder characterized mainly by progressive cerebellar degeneration, immunodeficiency, radiation sensitivity, genome instability, and predisposition to cancer. It is increasingly recognized that the premature aging component of A-T is an important driver of this disease, and A-T is therefore an attractive model to study the aging process. This review outlines the current state of knowledge pertaining to the molecular and cellular signatures of aging in A-T and proposes how these new insights can guide novel therapeutic approaches for A-T.

1. Introduction

Ataxia-telangiectasia (A-T) (OMIM#208900) is a genome instability syndrome caused by biallelic mutations in the ataxia-telangiectasia mutated (*ATM*) gene, exhibiting an incidence of ~1:40,000 - 1:300,000 live births in different communities world-wide (Taylor et al., 2019) and a median survival rate of ~25 years (Crawford et al., 2006; Perlman et al., 2012; Rothblum-Oviatt et al., 2016). *ATM*, located on the chromosomal region 11q22–23, encodes the multi-functional ATM protein kinase primarily known for orchestrating the cellular response to DNA double-strand breaks (DSBs) (Shiloh and Ziv, 2013). Although ATM's nuclear functions related to maintenance of genome stability remain the best understood aspect of ATM, its roles within the cytosolic cellular compartment have become an increasing point of interest (Hotokezaka et al., 2020; Chow et al., 2019; Stagni et al., 2018; Lee and Paull, 2020). Physiologically, the classical clinical picture of A-T parallels many aspects of human aging (Fig. 1). A-T is first presented by progressive cerebellar cortical degeneration that begins with deterioration and subsequent loss of Purkinje cells and ultimately affects other cell types leading to degeneration of the entire cerebellum. The cerebellar ataxia that reflects this process advances into a general motor dysfunction, ultimately limiting most A-T children to a wheelchair at the late stages of their first decade (Nissenkorn and Ben-Zeev, 2015). Immunodeficiency that includes the B- and T-cell lineages is another hallmark and is often accompanied by recurrent sinopulmonary infections. The multifaceted nature of A-T is further expressed in thymic degeneration, primary gonadal failure and occasional endocrine abnormalities (Crawford et al., 2006; Perlman et al., 2012; Rothblum-Oviatt et al., 2016). The striking predisposition to lymphoreticular malignancies is typical for the A-T patients throughout their lifespan while tendency to develop solid tumors may appear during the second and third decades of life. The acute sensitivity of A-T patients to the cytotoxic effect of ionizing radiation (IR) (Morgan et al., 1968) is reflected in cultured A-T cells as hypersensitivity to IR and radiomimetic chemicals, particularly those that induce double-strand breaks (DSBs) in the DNA (Taylor et al., 1975; Shiloh et al., 1983). Importantly, examination of A-T plasma analytes and a wide range of clinical abnormalities indicate a strong premature aging component associated with A-T pathology (reviewed in Shiloh et al., 2017).

Cellular and organismal aging are characterised by nine defined hallmarks: genome instability, telomere attrition, oxidative stress and mitochondrial dysfunction, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication (Lopez-Otin et al., 2013). Over the years, extensive efforts have been devoted to examining aging-related alterations in various *ATM* null systems and cells from A-T

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patients (Shiloh et al., 2017). This article comprehensively reviews the vast evidence for aging hallmarks reported thus far in A-T patients and A-T cultured cells (Fig. 2) and ties them to the known functions of ATM. We also point at potential treatment strategies targeting aging hallmarks that may prove beneficial for this currently untreatable condition.

2. Genome instability

Growing evidence supports the notion that accumulation of DNA damage over time is a fundamental driver of human aging (Schumacher et al., 2021; Vijg, 2021; Ribezzo et al., 2016; Barzilai et al., 2016). Both exogenous and endogenous threats incessantly challenge the integrity of DNA through damaging sources such as reactive oxygen species (ROS), DNA replication errors, environmental agents, and cancer treatments such as radiation therapy or chemotherapeutic drugs (Chatterjee and Walker, 2017a; Tubbs and Nussenzweig, 2017). These sources generate numerous forms of DNA damage that, if not repaired in a timely and proper manner, may lead to permanent scars in the form of mutations and chromosomal aberrations (Chatterjee and Walker, 2017b; Barnes et al., 2018). To cope with these threats, complex repair mechanisms have evolved that are capable of dealing with most types of DNA lesions – up to a certain amount (Jackson and Bartek, 2009). In mammalian cells, the DNA damage response (DDR) has evolved into a vast signalling system, which regulates DNA repair while activating special cell cycle checkpoints and modulating numerous cellular circuits (Colombo et al., 2020). The DDR temporarily recruits to its service numerous proteins from various cellular arenas and mobilizes massive protein relocation, post-translational modifications, and changes in protein stability and function (Hanawalt and Sweasy, 2020). This cascade is vigorously activated by DSBs (Goldstein and Kastan, 2015; Waterman et al., 2020; Jimeno et al., 2019). ATM is the major transducer in the DSB response: its kinase activity is enhanced in response to DSBs ("ATM activation") (Paull, 2015), and it phosphorylates more than 1100 targets (Matsuoka et al., 2007; Bensimon et al., 2010; Bensimon et al., 2011; Schlam-Babayov et al., 2021) in the numerous DDR branches. Notably, it was suggested that ATM also phosphorylates and modulates the activity of key players in the repair of DNA lesions other than DSBs, many of which are part of the daily wear and tear of nuclear DNA (Shiloh et al., 2017; Shiloh, 2014, 2020). Therefore, other than the abrogation of the DSB response, ATM's loss may affect the maintenance of genome

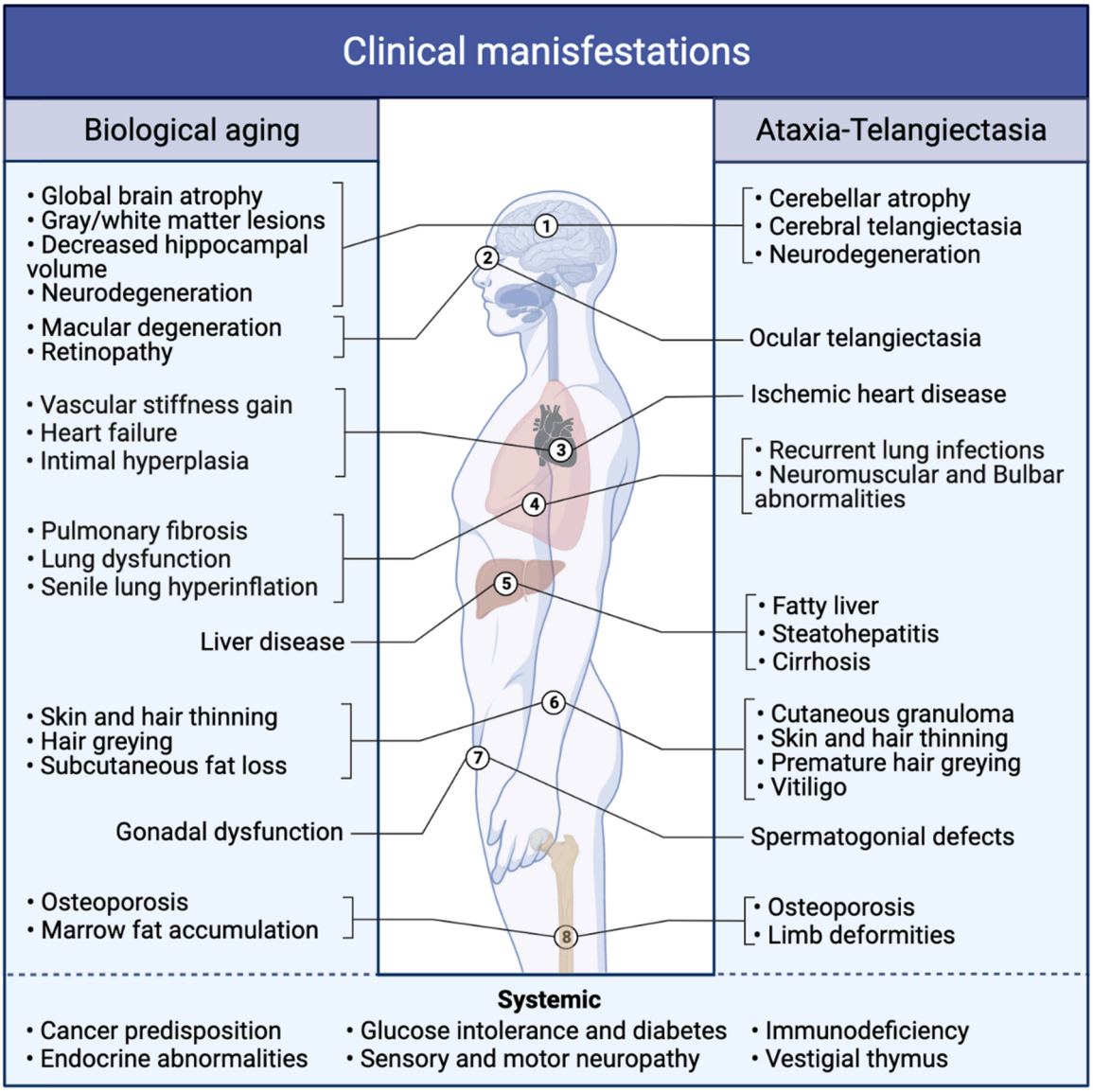

Fig. 1. Comparative schematic between the clinical pictures of human aging and A-T. Numbers indicate the major organs affected by A-T's premature aging condition and their associated clinical manifestations. (1) brain, (2) eyes, (3) heart, (4) lungs, (5) liver, (6) skin, (7) gonads and (8) bone.

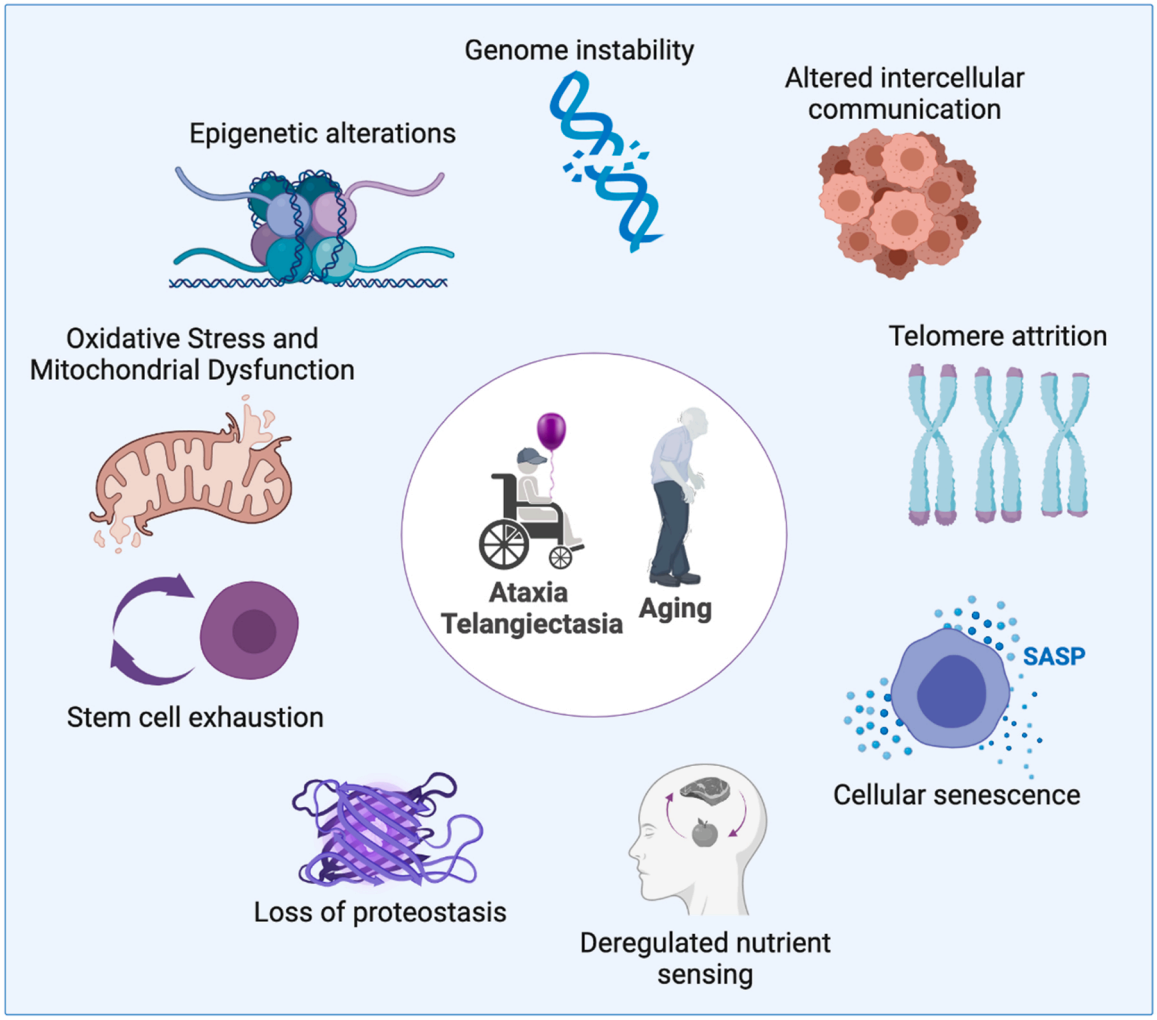

Fig. 2. The molecular and cellular hallmarks of A-T. These nine hallmarks – genome instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, oxidative stress and mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication – recapitulate the most significant features common to human aging and A-T, and putatively define the underlying mechanisms responsible for driving A-T's pathogenesis.

stability at large. Importantly, the efficiency of DNA repair mechanisms severely declines in aging (Petr et al., 2020). Furthermore, aging embodies the most important risk factor for the development of cancer (Adams et al., 2015) - a disease that often arises upon defective DNA repair and consequent generation of tumor-promoting *de novo* mutations (Balmain, 2020). A similar phenomenon is fundamentally accelerated in the aging process (Risques and Kennedy, 2018).

Given the chromosomal breakage and severe deficiency in maintenance of genome integrity in A-T, this genetic condition is included in the 'chromosome instability syndromes' - a group of disorders with inherent tendency for genome alterations that often result in a heightened predisposition to malignancy and other pathologies (Taylor et al., 2019). Despite their low median survival of ~25 years, A-T patients possess a lifetime cancer risk of 25%–40% (Suarez et al., 2015), a cancer risk one order of magnitude greater than the 3% reported for the human population under 25 years old (White et al., 2014). In fact, the inability to signal a DNA damage response and subsequent repair in A-T patients is most evident in their abnormally heightened sensitivity to the cytotoxic effects of ionizing radiation (Rothblum-Oviatt et al., 2016).

At the cellular level, studies of A-T patient-derived cells have demonstrated an exacerbated frequency in the levels of chromosomal translocations following radiation as well as spontaneous generation of chromosomal instability (Kojis et al., 1991; Bucher et al., 2021). In addition, A-T neurons and Atm-deficient mouse neurons reveal defective repair of DSBs and abrogated phosphorylation of ATM substrates (including H2AX-Ser139 or γH2AX, KAP1-Ser824 and CHK2-Thr68) (Carlessi et al., 2014; Stern et al., 2002; Biton et al., 2008; Dar et al., 2011; Tzur-Gilat et al., 2013; Tal et al., 2018). One intrinsic DNA damaging event that increases with aging is the reintegration of active retrotransposons – such as Long interspersed element-1 (LINE1) – into the human genome (Maxwell et al., 2011). LINE1 sequences alone comprise ~20% of the total mammalian genome and recent reports have shown a ~15-fold increase in the retrotransposition frequency of human LINE1 in ATM-deficient cells and an increase in LINE1 DNA copy number in post-mortem brain samples from A-T patients as compared to healthy counterparts (Coufal et al., 2011). Further studies in the brain of A-T patients have revealed a retrotransposition bias towards the integration into pre-existing repetitive elements (Jacob-Hirsch et al., 2018). Interestingly, these sites of somatic LINE1 integration contain a CCATT motif, a known DNA sequence that allows the recruitment of the human YY1 transcription factor to sites of DNA damage (Jacob-Hirsch et al., 2018). Although additional work is needed to better understand the potential impact of retrotransposon activity in A-T, the experimental data so far suggest a detrimental role of LINE1 in driving aberrantly high levels of retrotransposition and a subsequent increase of DNA damage and genome instability in A-T somatic cells.

In addition to its critical role in the DSB response, ATM also plays important roles in other homeostatic pathways that safeguard cells from other types of stresses (Stagni et al., 2018; Khoronenkova, 2016). These roles of ATM, described below, add further dimensions to the premature aging phenotype that is associated with its inactivation or genetic deletion.

3. Telomere attrition

While DNA damage tends to accumulate with age throughout the genome in a random fashion, telomeres are chromosomal regions that are particularly vulnerable to age-related deterioration (Armanios and Blackburn, 2012). Telomeres, nucleoprotein structures composed of repetitive DNA sequences bound by a multiprotein complex known as shelterin, are positioned at the end of linear chromosomes and their major function is to prevent DNA damage recognition at chromosome ends (O'Sullivan and Karlseder, 2010). Importantly, telomere sequences are lost from the ends of chromosomes in every cell division of somatic cells (Griffith et al., 1999). This is explained by the end- replication problem, a mechanism where DNA polymerases are unable to complete replication of linear DNA molecules (Watson, 1972). These DNA replication deficiencies and consequent telomere attrition ultimately lead to the onset of replicative senescence, also known as the Hayflick limit, a phenomenon that results in the limited proliferative capacity of most human somatic cells (Hayflick, 1965). Notably, this type of senescence initiation is caused by dysfunctional telomeres arising from critically short telomeres and altered telomere structures that not only induce a DDR signalling activation (d'Adda di Fagagna et al., 2003), but also embody irreparable genomic regions that sustain the detrimental senescence process (Fumagalli et al., 2012).

An initial finding related to A-T premature aging features was the observation of accelerated telomere shortening and increased telomere fusions in A-T peripheral blood lymphocytes (Metcalfe et al., 1996), cultured A-T patient fibroblasts (Smilenov et al., 1997; Xia et al., 1996) and cell lines expressing dominant-negative fragments of ATM (Smilenov et al., 1997). In fact, recent studies have showed that ATM inhibition directly induces telomere shortening in human cells, thereby indicating its role in regulating telomere length (Lee et al., 2015; Tong et al., 2015). In an effort to characterize the role of telomere shortening as a putative driver of A-T pathology, subsequent studies on A-T fibroblasts examined the ectopic expression of telomerase, a telomere-elongating ribonucleoprotein DNA polymerase complex. Interestingly, such experiments rescued both telomere shortening and a number of premature aging phenotypes of ATM-deficient cells (Wood et al., 2001; Naka et al., 2004), indicating telomere shortening is a contributor to the previously documented premature senescence of primary A-T fibroblasts (Shiloh et al., 1982). Moreover, concomitant depletion of Atm and the telomerase RNA component (Terc) in mice led to telomere dysfunction and subsequent accelerated aging as compared to control counterparts in which only Terc was depleted (Wong et al., 2003). While at first glance overexpression of telomerase would seem an attractive strategy for suppressing premature aging marks in A-T, effective long-term delivery and expression of telomerase is difficult and has been associated with an increased propensity for long-term tumorigenesis (Artandi et al., 2002), a risk already aggravated in A-T patients (Suarez et al., 2015). Alternative approaches include for instance the targeting of telomere transcripts via antisense oligonucleotides (ASOs) that are responsible for eliciting a telomeric DNA damage signalling (Rossiello et al., 2017; Nguyen et al., 2018), and that are known to aberrantly accumulate in a number of premature aging syndromes (Aguado et al., 2020, 2019). Due to A-T's characteristic telomere attrition and dysfunction, ASO-driven functional inhibition of telomeric non-coding RNAs may represent a potential therapeutic avenue to counteract the premature aging aspect of A-T.

4. Oxidative stress and mitochondrial dysfunction

Oxidative stress is a phenotype shared with premature aging syndromes and normal aging (Sies and Jones, 2020), and correlates with the notion that oxidative stress may contribute to the clinical manifestations of A-T. Indeed, a role for ATM in sensing and responding to oxidative stress was proposed soon after the identification of the *ATM* gene (Rotman and Shiloh, 1997) and subsequently obtained ample support from observations in human A-T cells and in Atm-deficient mice (reviewed in Shiloh, 2020; Barzilai et al., 2002). A landmark work in this field led to the discovery of a mechanism for ATM activation by oxidative stress, which is different from its canonical, DSB-induced activation (Guo et al., 2010a; Zhang et al., 2018). Subsequently, the spectrum of ATM targets following this mode of activation was found to differ from that of DSB-activated ATM (Kozlov et al., 2016), with ATM substrates playing roles in various physiological pathways including autophagy, mitochondrial homeostasis and proteostasis (Chow et al., 2019; Zhang et al., 2018; Tang et al., 2015; Alexander et al., 2010, 2010; Alexander and Walker, 2010; Berger et al., 2017; Kozlov et al., 2015; Lee et al., 2018). Importantly, reduced mitochondrial biogenesis and clearance combined with increased mitochondrial DNA damage, impaired apoptotic signalling, oxidative damage and diminished efficacy of the respiratory chain, all converge over time to aggravate the aging phenotype (Sun et al., 2016).

Within the cerebellum particularly, Atm-deficient mice displayed altered levels of the thiol-containing compounds groups glutathione and cysteine, increased activity of thioredoxin and manganese superoxide dismutase, and decreased catalase activity, all consistent with increased ROS production (Kamsler et al., 2001). Dihydroethidium oxidation imaging further demonstrated that increased superoxide levels were localised to Purkinje cells and nigral dopaminergic neurons in $Atm^{-/-}$ mice (Quick and Dugan, 2001).

In line with this, mitochondria in human A-T lymphoblastoid cells were abnormally distributed and displayed reduced membrane potential, respiration, and oxidation rates (Ambrose et al., 2007). Mitochondrial dysfunction was also confirmed in *ATM*-null thymocytes, while in wild type genotypes a portion of ATM protein was localised to the mitochondria where it rapidly becomes activated by mitochondrial dysfunction (Valentin-Vega et al., 2012). Furthermore, ATM loss resulted in increased ROS and higher numbers of aberrant mitochondria (Valentin-Vega et al., 2012). The authors provided evidence that the increased mitochondrial mass observed in ATM-deficient thymocytes was due to decreased clearance of damaged mitochondria by mitophagy, a process which was also found to be defective (Valentin-Vega et al., 2012), and that is also impaired in aging and age-related diseases (Chen et al., 2020a). Indeed, multiple evidence points to defective mitophagy in different A-T cell types. Stern et al., 2002 and subsequently Fang et al., 2016 showed depletion of NAD+ in ATM-deficient cells, which inhibited mitophagy and led to mitochondrial malfunction which was restored upon NAD+ repletion (Fang et al., 2016); ATM was shown to mediate spermidine-induced mitophagy in fibroblasts (Qi et al., 2016) and more recently nutrient deprivation in A-T led to a significant reduction in mitophagy which appeared to be due to a shift in the mitochondrial balance to fusion (Yeo et al., 2021a). Collectively, these findings suggest that failure to remove defective mitochondria is expected to interfere with normal mitochondrial function in A-T cells.

A specific pathway coupling ROS-mediated ATM activation and mitochondrial homeostasis is stimulated by mitochondrial-derived ROS and promotes the cell's antioxidant response by increasing the abundance and activity of glucose-6-phosphate dehydrogenase, thus increasing glucose metabolism via the pentose phosphate pathway and producing NADPH (Zhang et al., 2018; Guo et al., 2010b). In support of this, in rat cardiac myocytes Atm was consistently located to the inner mitochondrial membrane, and its chemical inhibition reduced oxidative phosphorylation at complex I and decreased NADH oxidation, resulting in lower levels of cellular NADPH (Blignaut et al., 2019). By acting as an

electron donor to glutathione and thioredoxin, NADPH functions as an antioxidant (Ren et al., 2017), thus a loss of functional ATM protein could jeopardise a cells' innate antioxidant defences, a process which is also known to decline with aging in multiple human tissues (Fernandez-Marcos and Nobrega-Pereira, 2016). This is also supported by the finding that ATP depletion activates ATM to modulate mitochondrial function through nuclear respiratory factor 1 (NRF1) (Chow et al., 2019). The mechanism appears to be through generation of ROS, which leads to ATM-dependent phosphorylation, dimerization, nuclear entry, up-regulation of mitochondrial genes to enhance the capacity of the electron transport chain and consequently mitochondrial function. The authors propose that in the absence of ATM, Purkinje cells are particularly susceptible to energy demands – due to their 62 times higher energy consumption than cerebral granule cells – and thus have high metabolic and ATM demands (Chow et al., 2019). While a common view is that defective maintenance of genome stability is responsible for the cerebellar degeneration in A-T (Shiloh, 2020), it is also possible that the particularly high demand for energy in Purkinje cells makes them susceptible and mitochondrial function may play an important role in the survival of these cells.

Antioxidant therapy options thus present attractive candidates to reduce oxidative stress-related symptoms of A-T. One example, isoindoline nitroxide, an antioxidant that mimics superoxide dismutase, when applied to mouse *Atm*$^{-/-}$ cultured Purkinje cells and to pregnant dams, protected against Purkinje cell death and neurodegeneration, enhanced dendritic branching, and reduced oxidative stress to wild type levels (Chen et al., 2003). In addition, catalase overexpression, targeted to mitochondria, reduced the incidence of thymic lymphomas in *Atm*$^{-/-}$ mice and partially rescued defects in memory T cells (D'Souza et al., 2013).

A role for ATM in regulating mitochondrial transfer between healthy and DNA-damaged cells has also recently been reported (Liu et al., 2021). Mitochondria and other small organelles can move between neighbouring cells, especially under stress conditions, facilitating direct communication and contributing to cell recovery. ATM-dependent, bilateral mitochondrial transfer was observed between healthy and irradiated fibroblasts, and subsequent fusion next allowed for the repair of irradiation-damaged mitochondria (Jin and Cordes, 2019). ATM-deficient cells were incapable of this process, although unilateral transfer was possible from controls to *ATM*$^{-/-}$ cells. Importantly, ATM was critically involved in this process and *ATM*$^{-/-}$ cells were incapable of supporting the survival of neighbouring DNA-damaged cells (Jin and Cordes, 2019).

Collectively, current available evidence in A-T models as well as patient cells strongly supports the idea that mitochondrial dysfunction contributes to A-T premature aging phenotypes and that antioxidant pharmacological interventions may ameliorate neuronal survival and the overall A-T detrimental clinical picture. However, the vast number of potential ATM targets in response to genotoxic and oxidative stresses (Matsuoka et al., 2007; Bensimon et al., 2010; Bensimon et al., 2011; Schlam-Babayov et al., 2021; Kozlov et al., 2015) indicates that the complete array of pathways downstream of ATM activation is far from exhaustive and their study may further contribute to a better understanding of the premature aging aspects of A-T.

5. Epigenetic alterations

The process of DNA compaction is highly dynamic, modulated by environmental conditions and drastically changes over the human lifespan (Zhang et al., 2020).

During the cell cycle interphase of germinal and somatic cells, there are two major compartments within chromatin: heterochromatin and euchromatin. The former adopts a tight structure that, for the most part, is transcriptionally silent. Even though heterochromatin constitutes a barrier to DNA repair factor recruitment to DNA-damaged *loci,* it remains permissive to DNA damage signalling, and this is thought to underlie its higher mutation rates (Fortuny and Polo, 2018). Repetitive regions such as telomeres, centromeres and retrotransposons embody constitutive heterochromatin, genomic regions that are frequently found attached to the nuclear envelope, often referred to as lamina-associated domains (LADs) (van Steensel and Belmont, 2017). The assembly of heterochromatin requires the trimethylation of H3K9, H4K20 and H3K27, often accompanied by extensive regions of CpG DNA methylation (Saksouk et al., 2015). Conversely, euchromatin is a more accessible genome conformation containing numerous active genes and generally is marked by H3K4me1 (predictive features of active enhancers), H3K4m3 (markers of transcription start sites) and H3K36me3 (enriched throughout highly transcribed regions) (Bannister and Kouzarides, 2011).

Recent studies have described epigenetic alterations occurring during the aging process. These changes span different layers of the epigenetic regulation, which include a global reduction of heterochromatin, nucleosome remodelling and loss, genome wide changes in histone post-translational modifications, DNA methylation changes, as well as re-localization of chromatin modifiers (Sen et al., 2016; Kane and Sinclair, 2019). Interestingly, despite the overall drop in heterochromatin content, specialized domains of facultative heterochromatin (named senescence-associated heterochromatin foci or SAHF) arise with age and contribute to the silencing of proliferation-promoting genes (such as E2F target genes) (Narita et al., 2003).

In the context of A-T pathology there is a global redistribution of heterochromatin as observed by micrographs of stained DNA and H3K27me3 (Grattarola et al., 2003). Interestingly, A-T patient-derived cells display elevated heterochromatin levels. This increase is the result of the stabilization of the H3K27 methyltransferase enhancer of zeste homolog 2 (EZH2), whose degradation is dependent on ATM-mediated phosphorylation. The relevance of this phenotype is evidenced by a lentiviral knockdown of EZH2 that rescues A-T deficiencies including Purkinje cell degeneration and behavioural abnormalities in *Atm*-null mice (Li et al., 2012). Furthermore, A-T patients' cerebella show a nuclear accumulation of histone deacetylase 4 (HDAC4). In healthy conditions, the bulk of HDAC4 protein remains in the cytoplasm in a phosphorylated state. Only when Protein phosphatase 2 (PP2A) removes this phosphate group, HDAC4 can be translocated to the nucleus, a process regulated through ATM by direct phosphorylation of PP2A. Given the intrinsic ATM deficiency in A-T, this represents an additional dysregulated epigenetic process present in A-T premature aging pathology (Li et al., 2012). During aging there is a decrease in the expression of the histone methyltransferase SUV39H1 in hematopoietic stem cells, leading to a reduction of H3K9 trimethylation (Djeghloul et al., 2016). One mechanism of degradation of the SUV39H1 protein is mediated by the ubiquitin-ligase MDM2. Interestingly, in hypoxic conditions ATM phosphorylates MDM2, thus preventing MDM2-mediated degradation of SUV39H1 (Likhatcheva et al., 2021). Given that this newly discovered mechanism is likely to be disrupted in A-T, it will be interesting to determine its contribution to A-T's premature aging phenotypes.

In addition to histone post-translational modifications, there is a general reduction of histone content with advanced age (O'Sullivan et al., 2010). Although this phenotype has not been directly addressed in A-T, RNA sequencing data from 2D cerebellar neurons derived from induced-pluripotent stem cells (iPSC) of A-T patients revealed a severe dysregulation of 14 histone genes (HIST3H2BA, HIST3H2BB, H2AFY, HIST1H3I, HIST1H4L, HIST1H4I, HIST1H2BO, HIST1H3A, HIST1H2BM, HIST1H4F, HIST1H1A, H2AFY2, HIST4H4 and H2AFJ) as compared to their healthy counterparts (Nayler et al., 2017).

DNA methylation patterns represent fundamental epigenetic traits that can be used to determine the aging process. DNA methylation deposition in humans is catalysed by three DNA methyltransferases (DNMT1, DNMT3a and 3b) and removal of this mark is mediated by the ten-eleven-translocation (TET) proteins (Sen et al., 2016). Across human aging tissues, an enrichment of methylation in CpG regions within

promoters of poorly expressed genes was found to be associated with a concomitant hypomethylation in regions outside these regulatory elements (Day et al., 2013). The robustness of these methylation patterns has defined the so-called "epigenetic clock", giving rise to a unified theory of life course (Horvath and Raj, 2018; Horvath, 2013). Interestingly, genome-wide DNA methylation profiling of peripheral blood mononuclear cells obtained from A-T patients revealed differential promoter methylation of 146 of these differentially expressed genes (McGrath-Morrow et al., 2020). Many of these genes were aging associated, including SERPINE1 (McGrath-Morrow et al., 2020), a protein elevated in conditions of insulin resistance and premature aging (Khan et al., 2017). In addition, a recent study has shown that 5-hydroxymethylcytosine (5hmc), a newly recognized epigenetic marker found at high levels in neurons, is significantly reduced in human A-T patients and *Atm*-null mouse cerebellar Purkinje cells (Jiang et al., 2015).

As discussed further, cellular senescence is a hallmark of aging. One of its characteristics is the formation of the SAHF; nuclear *foci* that are characterised by dense regions marked by heterochromatin protein 1 (HP1) content, H3K9me3, macroH2A and the high-mobility group A (HMGA) protein binding (Chandra and Narita, 2013). Interestingly, in cellular senescence there is also a non-stochastic heterochromatin redistribution that involves around 30% of the chromatin, including the LADs (Sedivy et al., 2008). Although the cellular senescence-related chromatin changes and SAHF components of A-T thus far have been scarcely characterised, growing efforts in characterising the genome-wide epigenetic changes in A-T have provided novel advances in our understanding of how A-T and other premature aging syndromes are associated with global epigenetic alterations characteristic of human aging.

6. Loss of proteostasis

The loss of protein homeostasis or proteostasis - a process that involves the correct synthesis, folding, stabilization and subsequent degradation of proteins - is considered a major driver of aging and age-related cellular dysfunction (Hipp et al., 2019; Sabath et al., 2020). This balance is primarily dependent on chaperones (proteins that catalyse the correct folding and stability of proteins) and two major degradation outlets: the autophagosomal-lysosome and ubiquitin-proteasome pathways, in which chaperones also participate. The failure to maintain this balance during the aging process prompts the onset of age-related diseases such as cardiac dysfunctions, cataracts, sarcopenia and neurodegenerative conditions including Alzheimer's disease (Labbadia and Morimoto, 2015). During the aging process, the protein conformation maintenance is challenged by factors such as acquired mutations and external stresses including ROS that favour the formation of aggregates or misfolded proteins (Klaips et al., 2018).

Cells from A-T patients exhibit a greater accumulation of ROS and mitochondrial damage that has been linked to the disruption of cellular proteostasis in these cells (Reichenbach et al., 2002; Poletto et al., 2017) (the role of mitochondrial problems in A-T aging hallmarks has been discussed above, see "Oxidative Stress and Mitochondrial Dysfunction''). Interestingly, in A-T there is a global increase in protein aggregation, and proteomic analysis of A-T patient lymphoblast cells reveals defects in global protein phosphorylation patterns (Lee et al., 2018). In fact, this phenotype is directly linked to an increase in poly-ADP-ribosylation brought about by ATM deficiency (Lee et al., 2021), a posttranslational modification that is known to attract disordered proteins and thus acts as a seed for their aggregation (Lee et al., 2021; Gupte et al., 2017). In terms of chaperone protein content, an increase in HSP27 and HSP60 in the serum of paediatric A-T patients compared to age-matched controls has been observed (Ozcelik et al., 2017).

Senescent cells exhibit a decrease in proteasome basal function that is associated with the accumulation of damaged proteins (Sabath et al., 2020; Sitte et al., 2000). Similarly, in A-T the ubiquitin-proteasome signalling pathway is dysregulated in patient-derived cells as well as in *Atm*-knockout mice (Wood et al., 2011). This phenotype was linked to ATM's role in inhibiting the ISG15 pathway, a signalling cascade that regulates proteasome-mediated protein turnover (Wood et al., 2011). As for the autophagosomal-lysosomal signalling pathway, aged human tissues exhibit transcriptional downregulation of many of its major players, including ATG5, ATG7 and BECLIN1 (Lipinski et al., 2010). In the context of A-T, autophagy and lysosomal trafficking are both deficient in ATM-deficient neurons and these insufficiencies were found to impact cellular functions such as synapse maintenance and neuronal survival (Cheng et al., 2020). In addition, transmission electron microscopy experiments in lymphocytes from A-T patients revealed accumulation of autophagosomes, further suggesting a disruption in the autophagy-lysosomal pathway upon ATM loss (D'Assante et al., 2017). Altogether, there is substantial evidence that A-T patients undergo aging-associated perturbed proteostasis, and experimental ablation of ATM can precipitate and recapitulate the characteristic loss of proteostasis in A-T.

7. Deregulated nutrient sensing

Aging is the major risk factor for metabolic diseases such as insulin resistance, type 2 diabetes mellitus, and other endocrine pathologies (Khosla et al., 2020) that are linked to dysregulation of nutrient-sensing pathways. Notably, A-T patients bear an increased risk of developing insulin resistance and type 2 diabetes early in life (Donath et al., 2020; Nissenkorn et al., 2016), and exhibit decreased brain glucose metabolism, as observed by positron emission tomography (Volkow et al., 2014). Mechanistic insights into the role of ATM in metabolic homeostasis originated from experiments showing that ATM depletion enhances the symptoms of metabolic syndrome in an apoE null mouse model of atherosclerosis. Treatment with chloroquine, a compound known to enhance ATM activity (Bakkenist and Kastan, 2003), was shown to improve the distinctive metabolic abnormalities observed in this model (Schneider et al., 2006).

One of the major regulators of nutrient-sensing in mammals is the somatotrophic axis, which is comprised of the growth hormone (GH) and the insulin-like growth factor 1 (IGF-1)/insulin signalling (IIS) pathway. The IIS is considered one the most conserved aging-controlling pathways, given that the levels of GH and IGF1 decline over time during aging (Junnila et al., 2013) and that downregulation of several of its targets (such as FOXO transcription factors, AKT, IGF1–1R and mTOR) affects the lifespan of different organisms, including humans (Liu and Sabatini, 2020). Interestingly, and similarly to what occurs in aging, A-T patients exhibit reduced serum levels of IGF-1 and IGFBP3 (Schubert et al., 2005) and undergo growth failure with concomitant decreased blood levels of GH (Voss et al., 2014). Indeed, since ATM is known to modulate the nutrient-sensing pathway by altering the expression of IGF1-IR in response to cellular stress (Shahrabani-Gargir et al., 2004), IGF-1 treatment has been proposed as a possible treatment for A-T patients (Fernandez et al., 2005). Furthermore, under stress conditions, ATM represses mTOR via activation of the LKB1/AMPK pathway, resulting in decreased mitochondrial activity and ROS levels (Alers et al., 2012). Interestingly, the downregulation or inhibition of mTOR extends the lifespan of multiple model organisms (Liu and Sabatini, 2020). Similarly, in ATM-deficient cells the increased ROS levels and mTOR activity are restored by the mTOR inhibitor Rapamycin (Alexander et al., 2010), a treatment that also ameliorates lymphomagenesis in Atm-deficient mice (Alexander et al., 2010).

Other sensors of nutrient scarcity and catabolism are the sirtuins. The sirtuins are a family of NAD-dependent protein deacetylases and ADP-ribosyltransferases that sense low-energy states by detecting high NAD+ levels (Houtkooper et al., 2010). Stern et al., 2002 first noticed an imbalance in pyridine nucleotides in *Atm-/-* brains, with a significant, progressive decrease in both the reduced and the oxidized forms of NAD. Notably, NAD+ depletion is a hallmark of aging tissues (Rajman et al.,

2018). Indeed, NAD supplementation improved lifespan and healthspan of Atm-deficient mice, while boosting intracellular NAD+ levels with nicotinamide riboside (NR) prevented senescence and improved motor function in Atm-deficient mice (Fang et al., 2016; Yang et al., 2021). Furthermore, SIRT1 increases healthspan by improving genomic stability (Herranz et al., 2010) and deacetylates, and thus activates, the PPARγ co-activator 1α (PGC-1α), orchestrating a metabolic response that includes mitochondrial biogenesis, enhanced anti-oxidant defences, and improved fatty acid oxidation (Rodgers et al., 2005). In addition, in Atm-deficient mice NAD+ increases the repair of DSBs through activation of Ku70 and DNA-PKcs with concomitant hyperactivation of the sirtuins (Fang et al., 2016). Importantly, there is recent evidence suggesting that ATM acts as a sensor of nutrient stress (Yeo et al., 2021a). In this study inhibition of glycolysis activated ATM, a process that appeared to be dispensable of DNA damage signalling given that minimal levels of γH2AX and phosphorylation of the ATM downstream substrate KAP-1 were detected. Conversely, there is also evidence that an increase in ROS brought about by ATM may be involved in activation of glycolysis (discussed above, see "Oxidative Stress and Mitochondrial Dysfunction''). The significance of this can be appreciated from the observation that in the absence of ATM cells are hypersensitive to glycolysis inhibition to the same degree as that observed when exposed to ionizing radiation and oxidative stress (Yeo et al., 2021a).

In response to oxidative stress ATM favours the pentose phosphate pathway, which in turn promotes the phosphorylation of Hsp27 and subsequent binding to glucose-6-phosphate dehydrogenase, ultimately increasing the production of NADPH and nucleotide synthesis required for DSB repair. Upon ATM ablation, the levels of these downstream products are reduced (Cosentino et al., 2011). Altogether, compelling evidence supports the instrumental role of ATM in balancing cellular and organismal nutrient sensing, a series of pathways that become deregulated in ATM deficiency in both animal models and A-T patients.

8. Cellular senescence

Cellular senescence is a process that often leads to irreversible cell cycle arrest, marked alterations in chromatin organization and numerous metabolic circuits, and a multi-faceted senescence-associated secretory phenotype (SASP) (Gorgoulis et al., 2019). Cell senescence plays a role in development and tissue homeostasis, as well as in age-related degenerative and malignant diseases (Rodier and Campisi, 2011; Campisi, 2013). It can be induced in proliferating cells in response to significant stress resulting from insults such as DNA damage, telomere attrition, mitochondrial dysfunction, oxidative stress or oncogene activation (Hernandez-Segura et al., 2018). Growing evidence reveals that the gradual accumulation of senescent cells over time contributes to organismal aging and drives co-morbidities such as cancer and chronic degenerative diseases (Gil, 2019; Calcinotto et al., 2019). Senescent cells often accumulate at sites of age-related pathologies and exert a significant detrimental impact on the normal physiology of the tissues, initiating a progressive functional deterioration (Martinez-Cue and Rueda, 2020; Katzir et al., 2021; Di Micco et al., 2021).

Senescent cells are variably characterized by combinations of morphological and biochemical characteristics none of which alone define this cell fate. Among these are activation of senescence-associated β-galactosidase (SA-β-Gal), nuclear shape alterations, senescence-associated heterochromatin foci (SAHF), increased DNA damage foci, loss of Lamin B1, upregulation of the cell cycle inhibitors, $p16^{INK4a}$ and $p21^{CIP1}$, increased p27, altered heterochromatin organization, and the SASP - secretion of a variable collection of growth factors, chemokines and inflammatory factors (Coppe et al., 2010).

Cellular senescence is also associated with a release of nuclear DNA fragments into the cytoplasm (Campisi, 2013; Ivanov et al., 2013; Dou et al., 2015). Such DNA fragments, also known as cytoDNA (Miller et al., 2021), are proposed to be formed due to DNA replication problems (Ho et al., 2016), defective DNA repair (Ahn et al., 2014), mitochondrial dysfunction (Vizioli et al., 2020) or accumulation of cytoplasmic reverse-transcribed retroelements (De Cecco et al., 2019). The presence of cytoDNA ultimately results in activation of the cGAS-STING signalling pathway (Dou et al., 2017; Gluck et al., 2017; Yang et al., 2017), a cytosolic DNA-sensing response that plays essential roles in activating pro-inflammatory SASP genes (Ishikawa and Barber 2008; Barber, 2015; Ishikawa et al., 2009). Notably, dysfunctional mitochondria not only have a direct effect on other cytoplasmic organelles in aging but also perturb the integrity of the nuclear genome through ROS retrograde signalling pathways, which ultimately drives cytoDNA formation and consequent initiation of pro-inflammatory gene expression in senescent cells (Vizioli et al., 2020).

A marked premature senescence of A-T primary fibroblast lines was first noted in the early 1980s (Shiloh et al., 1982) and was subsequently confirmed in various cell types from A-T patients (Wood et al., 2001; Naka et al., 2004; Barascu et al., 2012; Davis and Kipling, 2009; Park et al., 2013; Luo et al., 2014) (Fig. 3a). Cultured A-T fibroblasts were also found to harbour elevated levels of cytoDNA (Lan et al., 2019), a phenotype that appears dependent on DDR signalling deficiencies and that results in activation of pro-inflammatory pathways (Fig. 3b). Furthermore, mechanistic studies utilising olfactory neurosphere-derived cells from A-T patients demonstrate a detrimental role for ROS-JNK retrograde signaling pathway in instigating cytoDNA formation and hence the SASP (Aguado et al., 2021). While cytoDNA can be degraded by the autophagosome-lysosome machinery (Lan et al., 2019), this pathway is defective in A-T (Cheng et al., 2020) and thus may contribute to further cytoDNA accumulation in patient cells. In addition, studies in Atm-deficient mice demonstrated a role for cGAS and STING in priming a cytoDNA response, resulting in a systemic pro-inflammatory phenotype (Hartlova et al., 2015). Although senescence was not assessed in these mouse studies, it is noteworthy that multiple cytokines enriched in *Atm*-null mice are common to the SASP transcriptional signature. Of note, recent studies examining the consequences of short-term ATM inhibition in human wild type cells have recently reported increased (Chen et al., 2020b) and decreased (Kang et al., 2017) cellular senescence readouts upon exposure to the inhibitors. These results could either be explained by the fact that ATM inhibitors would prevent DNA damage-dependent ATM signalling and hinder senescence enforcement. On the other hand, inhibition of ATM results in defective repair and consequent increased DNA damage, inducing genome instability and ensuing acquisition of cellular senescence phenotypes. Future studies will help clarify this apparent incongruity.

Neurodegeneration remains as yet the most poorly understood aspect of A-T disease phenotypes (Rothblum-Oviatt et al., 2016; Shiloh, 2020; Biton et al., 2008). Focusing on the central nervous system, a recent study reported increased cellular senescence, and cytoDNA accumulation in the form of micronuclei in A-T patient-derived brain organoids as compared to wild type controls (Aguado et al., 2021). Some of the senescence hallmarks in these A-T brain organoids included high SA-β-gal activity, elevated $p21^{CIP1}$ and SASP expression, reduced Lamin B1 levels and increased nuclear shape abnormalities. Specifically, the authors demonstrated that senescent cells within A-T patient-derived brain organoids were enriched in astrocyte populations and exerted a pro-inflammatory cGAS-STING-dependent SASP induction (Fig. c). Importantly, pharmacological inhibition of either cGAS or STING in A-T brain organoids ameliorated multiple senescence signatures and improved neuronal synaptic activity and survival (Aguado et al., 2021). In line with this, a separate study using cultured astrocytes isolated from newborn *Atm*-knockout mice showed reduced cell proliferative capacity concomitant with accelerated onset of cellular senescence as independently measured by increased $p16^{INK4a}$ expression and SA-β-gal activity (Kim and Wong, 2009). In the same study the authors proposed that the premature senescence observed in Atm-deficient astrocytes was in part driven by increased ROS, as exemplified by the observation that anti-oxidant treatments delayed the initiation of the senescence process (Kim

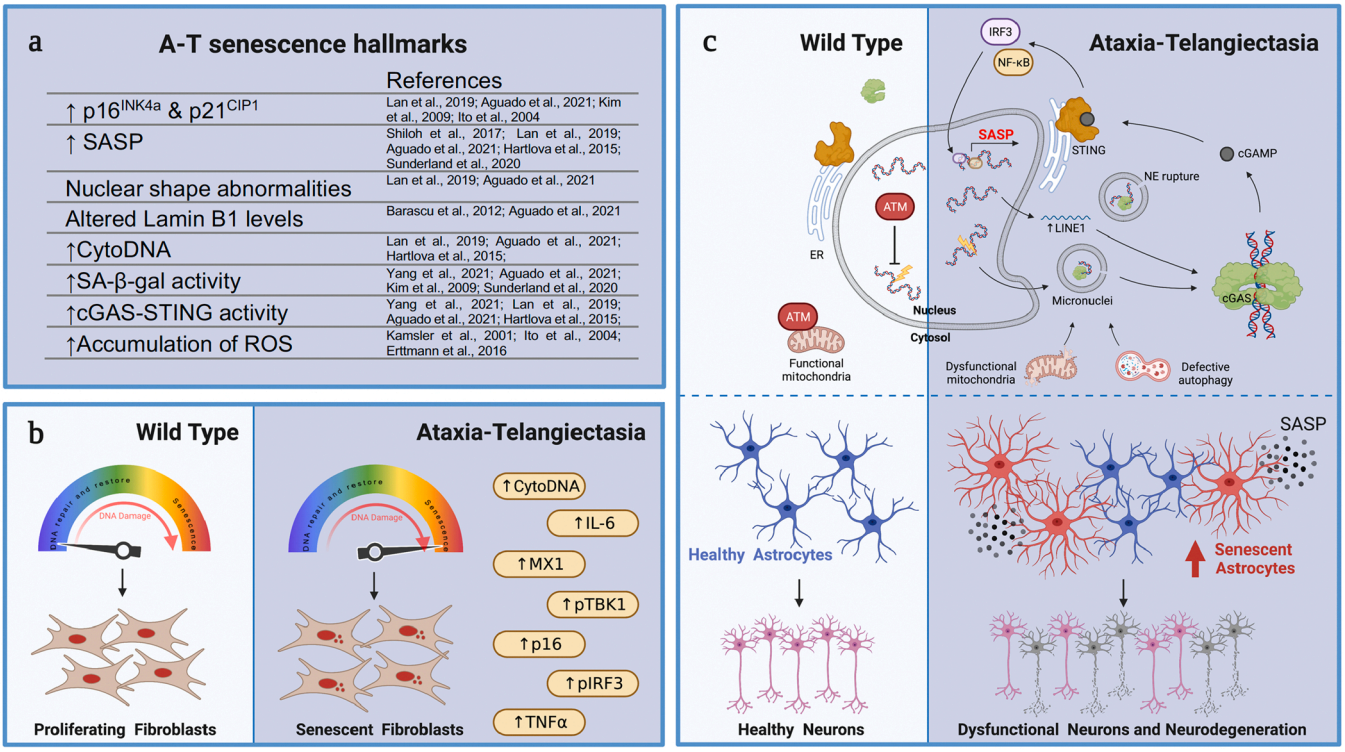

Fig. 3. Proposed models for cytoDNA-driven SASP activation in A-T. (a) Referenced evidence of hallmarks of senescence in A-T models and diverse patient cell types. (b) Genotoxic stress leads to DNA damage repair, accumulation of cytoDNA and cellular senescence in a manner dependant on the severity of DNA damage and the capacity of cells to elicit an efficient DDR. A-T fibroblasts undergo deficient DDR and therefore accumulate high levels of cytoDNA, ultimately leading to activation of pro-inflammatory pathways and premature onset of cellular senescence. (c) The schematic shows that upon ATM depletion, nuclear and/or mitochondrial DNA may mislocalize into the cytoplasm – giving rise to cytoDNA species – and activate cGAS. Nuclear shape abnormalities in A-T may lead to micronuclei formation; and when the nuclear envelope (NE) of micronuclei ruptures, the DNA content is exposed to cGAS surveillance. Other forms of cytoDNA such as DNA chromatin – for instance products arising from unresolved DNA damage, or LINE-1 reverse-transcribed complementary DNA – may also contribute to cGAS activation. Active cGAS dimerizes to synthesize 2′3′-cyclic GMP-AMP (cGAMP) from ATP and GTP. cGAMP in turn activates STING on the endoplasmic reticulum (ER) surface, which allows the phosphorylation and subsequent translocation of the transcription factors IRF3 and NF-κB into the nucleus to elicit the expression of the SASP.

and Wong, 2009). In addition, a separate report focusing on neural progenitor cells derived from A-T reprogrammed fibroblasts also showed increased SA-β-gal activity and IL-6 SASP production in cells positive for MAP2, a dendritically enriched protein and a marker of synaptic plasticity (Sunderland et al., 2020).

In summary, mounting evidence from multiple models of ATM deficiency and biopsy-derived patient lines suggests that cellular senescence arises as a response to chronic damage leading to a deleterious microenvironment that promotes premature acquisition of aging marks in A-T. Importantly, interventions that seek to prevent or delay cellular senescence, some of which belong to the so-called senomorphic and senolytic drug families (Di Micco et al., 2020) (such as cGAS and STING inhibitors), have shown encouraging outcomes and are emerging as important strategies with the capacity to halt neurodegenerative processes as well as to reduce the detrimental pro-inflammatory pathways associated with the SASP (Aguado and Wolvetang, 2022). An additional trigger of the SASP in senescence is the accumulation of aberrantly elevated cytoplasmic LINE1 reverse-transcribed retroelements, which are recognised by cGAS and STING in a sequence-unspecific manner to drive interferon responses (Gorbunova et al., 2021). Importantly, blocking LINE1 transcription using inhibitory RNA molecules or via inhibition of LINE1 reverse transcription with the drug Lamivudine prevents this interferon SASP response in senescent cells (De Cecco et al., 2019). Given that A-T patient cells exert a higher frequency in LINE1 retrotransposition (Coufal et al., 2011) (discussed above, see "Genomic Instability''), it is conceivable that future studies using therapeutics targeting LINE1 activity –such as Lamivudine, Emtricitabine or Tenofovir– in combination with senomorphic compounds that target the cGAS-STING pathway may yield beneficial outcomes in A-T cells, by delaying their characteristic premature entry into cellular senescence and their associated detrimental paracrine effects, including the SASP.

9. Stem cell exhaustion

The progressive decline in the regenerative capacity of human tissues has emerged as a prominent feature of aging. Adult stem cells are fundamental to the processes of tissue replenishing and maintenance of normal organ function and damaged tissue regeneration (Post and Clevers, 2019). However, during physiological aging tissue-resident stem cells decline in number and function, and show an increased propensity to enter senescence, which jeopardizes their regenerative capacity, and thus may contribute to tissue loss and degeneration (Ermolaeva et al., 2018).

In A-T, there is compelling evidence that a lack of ATM leads to profound disruptions in the stem cell niche. In the central nervous system (CNS), ATM absence appears to significantly impact human neural stem cell (NSC) differentiation. While the differentiation rates towards MAP2 and β-Tubulin III-positive neurons remains unaffected by ATM ablation, the yield of GABAergic neurons is severely compromised (Carlessi et al., 2013) and inversely, astrocytic commitment is abnormally favored (Aguado et al., 2021). In addition, the expression of neuronal maturation and synaptic markers including SCG10, SYP and PSD95 is notably deregulated (Carlessi et al., 2014), although A-T neurons display similar action potential discharges as their control counterparts.

Further to the functional abnormalities of stem cell observed in the CNS of A-T, a reduced ability of hematopoietic stem cells (HSCs) to divide and differentiate into lymphocyte progenitor cells in the developing bone marrow has been reported. Specifically, ATM's role in regulating ROS was shown to be essential to facilitate HSC self-renewal, and its genetic ablation led to the upregulation of $p16^{INK4a}$ and HSC dysfunction (Ito et al., 2004). Importantly, in vivo treatment with N-acetyl-L-cysteine (an antioxidant agent) restored the regenerative capacity of Atm-deficient HSCs in mice, ultimately preventing bone marrow failure (Ito et al., 2004). Furthermore, lack of ATM leads to impaired T lymphocyte maturation and accumulation of immature cells in the thymus (Matei et al., 2007). In fact, the functional response to ROS in the thymus is compromised in the absence of ATM activity (Ito et al., 2007), further reinforcing the detrimental role of ROS in driving HSC dysfunction in A-T. Similar to the phenotypes observed in aging and premature aging syndromes, A-T patients also display bone deficiencies including osteoporosis/osteopenia and low vitamin D levels (Rothblum-Oviatt et al., 2016).

To understand these deficiencies at the cellular level, experiments in Atm-deficient mice examined the role of adult stem cells in bone tissue replenishing. Interestingly, osteoclastogenesis and colony formation assays using bone marrow cells derived from *Atm*-null mice yielded equivalent results compared to wild type counterparts (Hishiya et al., 2005), suggesting no defects in bone resorption. In contrast, Atm-deficient mice showed reduced bone tissue formation due to proliferation defects in mesenchymal stem cell progenitor cells (Hishiya et al., 2005). These deficiencies mechanistically involved the hyperphosphorylation of p38 – a molecular driver of cellular senescence (Anerillas et al., 2020) – as well as a significant reductions in the levels of the IGF-1 receptor in bone marrow cells of *Atm-/-* mice (Hishiya et al., 2005).

The germline is likewise susceptible to the aging process, including for instance spermatogonial stem cell dysfunction, a process that leads to a progressive loss of sperm-forming potential that is accompanied by abnormal proliferation and major epigenetic alterations (Kanatsu-Shinohara et al., 2019). Fundamentally, spermatogenesis is sustained by the reconstitutive capacity of undifferentiated spermatogonial populations (Takubo et al., 2008). Interestingly, in Atm-deficient mice a progressive decline in undifferentiated spermatogonia is observed that is accompanied by the acquisition of cell-cycle arrest phenotypes both in vitro and in vivo (Takubo et al., 2008). Specifically, this checkpoint arrest activation in undifferentiated *Atm*-null spermatogonia is driven by increased DNA damage, as measured by Comet assay, and the upregulation of the $p19^{ARF}$-p53-$p21^{CIP1}$ axis pathway. Importantly, genetic depletion of $p21^{CIP1}$ in an *Atm*-null background restored the stem cell capacity of undifferentiated spermatogonia by overcoming the DNA damage-induced checkpoint arrest, indicating that ATM also plays fundamental roles in preserving germ line stem cell self-renewal (Takubo et al., 2008).

10. Altered intercellular communication

While cell-intrinsic changes constitute a fundamental trait of the aging process, defects at the level of intercellular communication likewise contribute to organismal aging (Fafian-Labora and O'Loghlen, 2020). Chronic inflammation, often referred to as "inflammaging", is a consequence of abnormal intercellular communication and may arise from increased tissue damage, enhanced activation of the NF-kB transcription factor, progressive gain in defective autophagy, or deficiencies in immune clearance of pathogens and dysfunctional host cells (Franceschi et al., 2018). Interestingly, whole-body elimination of senescent cells reduces the systemic levels of proinflammatory cytokines (Baker et al., 2016), suggesting that the SASP arising from cellular senescence is a strong contributor to "inflammaging". Of note, inflammation is also involved in the pathogenesis of type 2 diabetes, a condition that is common to both human aging and A-T (see "Deregulated Nutrient Sensing'').

Analyses of the transcriptional signatures of patient biopsies emphasize the relevance of detrimental pro-inflammatory pathways in A-T (McGrath-Morrow et al., 2018). Interestingly, nuclear translocation and consequent activation of NF-kB is detected in rodent models of A-T (Quek et al., 2017; Song et al., 2019), a phenomenon also observed in A-T patient-derived brain organoids and that also display enrichment of transcriptional signatures related to NF-kB-dependant inflammation (Aguado et al., 2021). Furthermore, cells from A-T patients and Atm-deficient mice undergo diminished inflammasome activation leading to impaired anti-bacterial innate immunity (Erttmann et al., 2016). This is particularly relevant since a major cause of mortality in A-T is respiratory bacterial infections. Mechanistically, Atm absence impairs NLRC3 and NLRC4 inflammasomes via ROS, highlighting a vital role for oxidative stress – putatively stemming from dysfunctional mitochondria – in the negative regulation of inflammasomes and ensuing anti-bacterial immunity (Erttmann et al., 2016).

Sirtuins also have a major influence on inflammatory responses associated with aging (Imai and Guarente, 2016). SIRT1, a protein deacetylase dependent on NAD^+, plays a protective role in dampening inflammation-related genes. This occurs via suppression of NF-κB signalling through deacetylation of the p65 subunit of NF-κB (Yeung et al., 2004). Given the observed NAD^+ depletion and subsequent reduction in SIRT1 activity in A-T, it is conceivable that their abnormally low levels may directly contribute to NF-κB hyperactivation. Supporting this postulate, boosting intracellular NAD^+ levels via NR supplementation reduces the characteristic chronic inflammation present in the brain of Atm null mice (Yang et al., 2021). On the other hand, a direct role for ATM has been identified involving downregulation of La ribonucleoprotein domain family member 7 (LARP7), a 7SK RNA binding protein and antagonist of aging (Yan et al., 2021). ATM activation triggers the extracellular shuttling and downregulation of LARP7, leading to dampening of SIRT1 deacetylase activity and enhancing p53 and NF-κB transcriptional activity to accelerate cellular senescence (Yan et al., 2021). Likewise, SIRT6 is also found to exert anti-inflammatory effects (Imai and Guarente, 2016) and plays a role in DDR sensing (Onn et al., 2020). Notably, the phosphorylation of SIRT6 – a direct ATM target – is essential to preserve SIRT6 stability and bypasses MDM2-mediated ubiquitination and proteasomal degradation (Qian et al., 2018). Furthermore, additional gene copies of Sirt6 extend the lifespan and restore metabolic deficiencies in Atm-deficient mice. Importantly, low dose treatment with chloroquine, known to activate ATM, promotes enhanced SIRT6 activity and reduces systemic inflammation in a progeric mouse model (Qian et al., 2018). Altogether, mounting evidence indicates that the hallmarks of aging in A-T are not limited to merely cell-intrinsic phenomena but also extend to broad alterations in intercellular communication alterations that may allow novel therapeutic opportunities for modulating premature aging at the organismal level in A-T.

11. Interventions and hallmarks crosstalk

While the pathophysiology and molecular mechanisms that portray A-T's clinical picture span all hallmarks of aging, their capacity to interrelate is remarkable. These hallmarks in fact, rather than nine independent factors driving the aging process, are highly intertwined processes, and elucidating the interplay between these is critical to understanding A-T's premature aging phenotypes. Interventions targeting individual hallmarks of aging represent mechanistic opportunities to interrogate the interdependency among A-T aging hallmarks. Consequently, in the recent years various strategies have been developed using a combination of in vitro models of senescence and in vivo accelerated aging animal models, some of which represent putative interventions for targeting aging processes in A-T (Table 1). For instance, the use of antiretroviral drugs blocking LINE-1 activity transcends their capacity to prevent DNA damage via self-copy and reintegration at new

Table 1
| Proposed interventions targeting A-T aging hallmarks.

Putative intervention	Targets	Dysregulated phenotype in A-T	*In vitro* dose	*In vivo* dose	Refs
Lamivudine	LINE-1	Increased LINE-1 retrotransposition	7.5 μM	* 2 mg ml^{-1}	(Coufal et al., 2011; De Cecco et al., 2019)
Telomerase	Telomeres	Accelerated telomere shortening	–	–	(Wood et al., 2001; Naka et al., 2004; Wong et al., 2003)
Telomeric antisense oligonucleotides	Telomeric non-coding RNA	Dysfunctional telomeres	20 nM	15 mg kg^{-1}	(Rossiello et al., 2017; Aguado et al., 2019; Michelini et al., 2018)
Tazemetostat	EZH2	Increased H3K27me3	1 μM	125 mg kg^{-1}	(Grattarola et al., 2003; Li et al., 2012)
Trichostatin A	HDAC4	Nuclear accumulation of HDAC4	10 μM	10 mg kg^{-1}	(Li et al., 2012)
Veliparib	PARP	Cerebellar protein aggregation	10 μM	12.5 mg kg^{-1}	(Lee et al., 2021)
IGF-1	Insulin signalling pathway	Reduced systemic IGF-1, IGFBP3 and GH blood levels	–	–	(Schubert et al., 2005; Voss et al., 2014; Fernandez, 1 et al., 2005)
Rapamycin	mTOR	Increased ROS and mTOR activity	0.2 μM	15 mg kg^{-1}	(Alexander et al., 2010)
Nicotinamide riboside	NAD+	Deficient mitophagy	500 μM	* 12 mM	(Fang et al., 2016; Yang et al., 2021)
N-acetyl-L-cysteine	ROS	Increased ROS in stem cell niche and inflammasome defects	25–100 μM	100 mg kg^{-1}	(Ito et al., 2004; Erttmann et al., 2016)
Glutathione	ROS	Inflammasome activation defects	–	–	(Erttmann et al., 2016)
Acetylsalicylic acid	cGAS	CytoDNA	4 mM	50 mg kg^{-1}	(Aguado et al., 2021; Dai et al., 2019)
H-151	STING	CytoDNA	3 μM	4 mg kg^{-1}	(Aguado et al., 2021; Haag et al., 2018)
CCCP	STING	CytoDNA	50 μM	–	(Song et al., 2019)
SP600125	JNK	CytoDNA	20 μM	50 mg kg^{-1}	(Vizioli et al., 2020; Aguado et al., 2021)
MitoQ	ROS-JNK signalling	Cytoplasmic DNA accumulation	20 nM	* 250 μM	(Vizioli et al., 2020; Aguado et al., 2021)
PD98059	ERK	Increased ROS	50 μM	10 mg kg^{-1}	(Kim and Wong, 2009)
Betamethasone	Glucocorticoid receptors	Elevated inflammatory signatures	10–1000 nM	30 μg kg^{-1}	(Quek et al., 2017)
Ibuprofen	Cyclooxygenase	Elevated inflammatory signatures	200 μM	62.5 mg kg^{-1}	(Hui et al., 2018)
SB230580	p38	p38-driven cellular senescence	10 μM	–	(Davis and Kipling, 2009)
Triheptanoin	Mitochondria	Mitochondrial dysfunction	750 μM	–	(Yeo et al., 2021b)

LINE-1, Long interspersed element-1; EZH2, Enhancer of zeste homolog 2; IGF-1, Insulin-like growth factor 1; IGFBP3, IGF binding protein-3; GH, Growth hormone; mTOR, mammalian target of rapamycin; ERK, extracellular signal-regulated kinase; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; NAD, Nicotinamide adenine dinucleotide; cGAS, cyclic GMP–AMP synthase; STING, stimulator of interferon genes; PARP; Poly-ADP-ribose Polymerase. *Intervention administered in drinking water.

sites in the genome. Given that LINE-1 retrotransposition relies on intermediate cytosolic DNA reverse-transcribed elements, the inhibition of this process also alleviates cytoDNA-responsive cGAS/STING pathways and ensuant transcription of the SASP (De Cecco et al., 2019). Thus, although the primary consequence of LINE-1 *de novo* self-integration results in increased genome instability, other hallmarks including cellular senescence and SASP-dependant intercellular communication are consequently affected. The use of the HDAC4 inhibitor trichostatin A (TSA) further highlights this crosstalk among hallmarks. While the defective nuclear accumulation of HDAC4 and consequent epigenetic alterations in vivo can be prevented by TSA injection in ATM null mice, HDAC4 inhibition impacts multiple A-T phenotypes related to senescence and genome instability. These include restored cell cycle marker levels, improved cerebellar neuron survival and locomotor activity, and reduced neuronal DNA damage (Li et al., 2012).

Other putative interventions that impact multiple symptomatic features of aging are for instance those with the capacity to modulate ATM-independent telomere dysfunction signalling. ASOs targeting telomeric damage-induced long ncRNAs not only prevent site-specific DNA damage signalling, but also block a DDR-dependent SASP secretome and ensuant tissue immune infiltrates, thus affecting multiple downstream hallmarks (Aguado et al., 2019). Importantly, suppression of mitochondrial ROS or inhibition of JNK signalling attenuates cytoDNA formation, DNA damage accumulation and SASP expression in senescent cells (Vizioli et al., 2020), a phenomenon also observed in A-T patient cells (Lan et al., 2019; Aguado et al., 2021) further highlighting the interconnectivity among hallmarks. Given A-T cells' characteristic altered nutrient sensing and sensitivity to metabolic stress, interventions targeting these have recently been tested. Triheptanoin, a triglyceride containing three odd chain fatty acid heptanoate molecules, was recently found to correct various defective pathways present in A-T, including aberrant endoplasmic reticulum-mitochondrial signalling, mitochondrial dysfunction and mitochondrial autophagy; a strategy currently tested in an ongoing clinical trial in A-T patients (Yeo et al., 2021b). Furthermore, dysregulation of mTOR represents an additional altered nutrient sensing phenotype in A-T that can be attenuated by rapamycin treatment, an intervention that concomitantly rescues mitochondrial dysfunction-induced ROS (Alexander et al., 2010). In fact, ROS inhibition by either N-acetyl-L-cysteine or catalase in A-T mouse models in turn reduces $p16^{INK4a}$ and $p19^{ARF}$ markers, cellular senescence phenotypes that were found to ultimately induce stem cell dysfunction (Ito et al., 2004). Notably, the use of PARP inhibitors has made possible the connection between DNA damage and pathological self-assembly of intrinsically disordered proteins in ATM deficiency (Lee et al., 2021). In fact, it appears that upon ROS-induced single-strand DNA break generation in A-T cells, insoluble protein species arise at PAR-associated genomic sites, indicating a dependency of loss of proteostasis phenotypes on elevated oxidative stress and genome instability (Lee et al., 2021).

While certain aging hallmarks such as genome stability, senescence, and oxidative stress and mitochondrial dysfunction appear to preferentially play central roles in driving aging processes in A-T; the published data supports a theory of aging mechanisms where these hallmarks – and possibly others yet to be discovered – collectively and synergistically contribute the A-T's premature aging pathology.

12. Conclusions and future perspectives

Patient cells as well as cellular and mouse models have greatly advanced our understanding of the molecular drivers of premature aging disorders and have provided novel insights into the drivers of human aging. Over recent years, the functional characterization of the accelerated aging phenotypes of A-T in a similar range of model systems has not only revealed that ATM absence affects each of the major hallmarks of aging, but also provided insights into their connectivity, as outlined in this review. This broad impact of ATM deficiency on the aging process is both a function of the large number of protein targets that are phosphorylated by ATM as well as its multifunctional role in orchestrating DNA damage responses in the nucleus and its antioxidant response and metabolic roles in the cytoplasm, including mitochondria. Indeed, it is

becoming increasingly clear that ATM plays crucial roles in balancing and fine-tuning metabolic and mitochondrial redox homeostasis processes with nuclear DNA damage and epigenetic responses - molecular processes that have well-understood interlinked roles in cellular senescence and organismal aging. As pointed out above, accumulation of senescent cells with time not only fuels the aging process but also drives co-morbidities such as cancer and chronic degenerative diseases. One of the major hallmarks of aging is mitochondrial dysfunction, and as indicated above there is compelling evidence for this in a variety of ATM-deficient cells. This is manifested by abnormalities in energy metabolism and mitophagy and the likely accumulation of abnormal mitochondria which would impact on cellular behaviour. The allelic loss of the autophagic gene *Becn1* and its ability to delay tumorigenesis suggests that this is occurring by altering mitochondrial abnormalities rather than improving the DNA damage response.

Remarkably, while genetic depletion of ATM results in a significant decrease in lifespan and healthspan (Fang et al., 2016), increased ATM kinase activity in vivo has the opposite effect (Qian et al., 2018). This accentuates the pro-longevity role of ATM, highlights A-T's unique progeroid hallmarks and reinforces the notion that A-T is an important model for studying the molecular drivers of human aging. In this review, we have appraised the latest findings made using ATM-deficient cultured cells as well as in vivo models of A-T, highlighting emerging therapeutic opportunities that may ameliorate the phenotypes that underpin A-T premature aging. This is a fine example of the span of insights into human biology that can be obtained from studying rare genetic disorders and the broad biomedical implications of these studies.

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Competing interests

The authors declare no competing interests.

References

Adams, P.D., Jasper, H., Rudolph, K.L., 2015. Aging-induced stem cell mutations as drivers for disease and cancer. Cell Stem Cell 16 (6), 601–612. https://doi.org/10.1016/j.stem.2015.05.002.

Aguado, J., Wolvetang, E.J., 2022. Exploring aging interventions in human brain organoids. Aging 14 (4), 1592–1593. https://doi.org/10.18632/aging.203925.

Aguado, J., Sola-Carvajal, A., Cancila, V., et al., 2019. Inhibition of DNA damage response at telomeres improves the detrimental phenotypes of Hutchinson-Gilford Progeria Syndrome. Nat. Commun. 10 (1), 4990. https://doi.org/10.1038/s41467-019-13018-3.

Aguado, J., d'Adda di Fagagna, F., Wolvetang, E., 2020. Telomere transcription in ageing. Ageing Res Rev. 62, 101115 https://doi.org/10.1016/j.arr.2020.101115.

Aguado, J., Chaggar, H.K., Gomez-Inclan, C., et al., 2021. Inhibition of the cGAS-STING pathway ameliorates the premature senescence hallmarks of Ataxia-Telangiectasia brain organoids. Aging Cell, e13468. https://doi.org/10.1111/acel.13468.

Ahn, J., Xia, T., Konno, H., Konno, K., Ruiz, P., Barber, G.N., 2014. Inflammation-driven carcinogenesis is mediated through STING. Nat. Commun. 5, 5166. https://doi.org/10.1038/ncomms6166.

Alers, S., Loffler, A.S., Wesselborg, S., Stork, B., 2012. Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks. Mol. Cell Biol. 32 (1), 2–11. https://doi.org/10.1128/MCB.06159-11.

Alexander, A., Walker, C.L., 2010. Differential localization of ATM is correlated with activation of distinct downstream signaling pathways. Cell Cycle 9 (18), 3685–3686. https://doi.org/10.4161/cc.9.18.13253.

Alexander, A., Cai, S.L., Kim, J., et al., 2010. ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. Proc. Natl. Acad. Sci. USA 107 (9), 4153–4158. https://doi.org/10.1073/pnas.0913860107.

Alexander, A., Kim, J., Walker, C.L., 2010. ATM engages the TSC2/mTORC1 signaling node to regulate autophagy. Autophagy 6 (5), 672–673. https://doi.org/10.4161/auto.6.5.12509.

Ambrose, M., Goldstine, J.V., Gatti, R.A., 2007. Intrinsic mitochondrial dysfunction in ATM-deficient lymphoblastoid cells. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. Hum. Mol. Genet. 16 (18), 2154–2164. https://doi.org/10.1093/hmg/ddm166.

Anerillas, C., Abdelmohsen, K., Gorospe, M., 2020. Regulation of senescence traits by MAPKs. Geroscience 42 (2), 397–408. https://doi.org/10.1007/s11357-020-00183-3.

Armanios, M., Blackburn, E.H., 2012. The telomere syndromes. Nat. Rev. Genet. 13 (10), 693–704. https://doi.org/10.1038/nrg3246.

Artandi, S.E., Alson, S., Tietze, M.K., et al., 2002. Constitutive telomerase expression promotes mammary carcinomas in aging mice. Proc. Natl. Acad. Sci. USA 99 (12), 8191–8196. https://doi.org/10.1073/pnas.112515399.

Baker, D.J., Childs, B.G., Durik, M., et al., 2016. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530 (7589), 184–189. https://doi.org/10.1038/nature16932.

Bakkenist, C.J., Kastan, M.B., 2003. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature 421 (6922), 499–506. https://doi.org/10.1038/nature01368.

Balmain, A., 2020. The critical roles of somatic mutations and environmental tumor-promoting agents in cancer risk. Nat. Genet 52 (11), 1139–1143. https://doi.org/10.1038/s41588-020-00727-5.

Bannister, A.J., Kouzarides, T., 2011. Regulation of chromatin by histone modifications. Cell Res. 21 (3), 381–395. https://doi.org/10.1038/cr.2011.22.

Barascu, A., Le Chalony, C., Pennarun, G., et al., 2012. Oxidative stress induces an ATM-independent senescence pathway through p38 MAPK-mediated lamin B1 accumulation. Research Support, Non-U.S. Gov't. EMBO J. 31 (5), 1080–1094. https://doi.org/10.1038/emboj.2011.492.

Barber, G.N., 2015. STING: infection, inflammation and cancer. Nat. Rev. Immunol. 15 (12), 760–770. https://doi.org/10.1038/nri3921.

Barnes, J.L., Zubair, M., John, K., Poirier, M.C., Martin, F.L., 2018. Carcinogens and DNA damage. Biochem Soc. Trans. 46 (5), 1213–1224. https://doi.org/10.1042/BST20180519.

Barzilai, A., Schumacher, B., Shiloh, Y., 2016. Genome instability: linking ageing and brain degeneration. Mech. Ageing Dev. https://doi.org/10.1016/j.mad.2016.03.011. Mar 31.

Barzilai, A., Rotman, G., Shiloh, Y., 2002. ATM deficiency and oxidative stress: a new dimension of defective response to DNA damage. DNA Repair 1 (1), 3–25. https://doi.org/10.1016/s1568-7864(01)00007-6.

Bensimon, A., Schmidt, A., Ziv, Y., et al., 2010. ATM-dependent and -independent dynamics of the nuclear phosphoproteome after DNA damage. Sci. Signal 3 (151), rs3. https://doi.org/10.1126/scisignal.2001034.

Bensimon, A., Aebersold, R., Shiloh, Y., 2011. Beyond ATM: the protein kinase landscape of the DNA damage response. FEBS Lett. 585 (11), 1625–1639. https://doi.org/10.1016/j.febslet.2011.05.013.

Berger, N.D., Stanley, F.K.T., Moore, S., Goodarzi, A.A., 2017. ATM-dependent pathways of chromatin remodelling and oxidative DNA damage responses. Philos. Trans. R. Soc. Lond. B Biol. Sci. 372 (1731) https://doi.org/10.1098/rstb.2016.0283.

Biton, S., Barzilai, A., Shiloh, Y., 2008. The neurological phenotype of ataxia-telangiectasia: solving a persistent puzzle. DNA Repair (Amst.) 7 (7), 1028–1038. https://doi.org/10.1016/j.dnarep.2008.03.006.

Blignaut, M., Loos, B., Botchway, S.W., Parker, A.W., Huisamen, B., 2019. Ataxia-Telangiectasia Mutated is located in cardiac mitochondria and impacts oxidative phosphorylation. Sci. Rep. 9 (1), 4782. https://doi.org/10.1038/s41598-019-41108-1.

Bucher, M., Endesfelder, D., Roessler, U., et al., 2021. Analysis of chromosomal aberrations and gammaH2A.X foci to identify radiation-sensitive ataxia-telangiectasia patients. Mutat. Res. 861–862. https://doi.org/10.1016/j.mrgentox.2020.503301.

Calcinotto, A., Kohli, J., Zagato, E., Pellegrini, L., Demaria, M., Alimonti, A., 2019. Cellular senescence: aging, cancer, and injury. Physiol. Rev. 99 (2), 1047–1078. https://doi.org/10.1152/physrev.00020.2018.

Campisi, J., 2013. Aging, cellular senescence, and cancer. Annu Rev. Physiol. 75, 685–705. https://doi.org/10.1146/annurev-physiol-030212-183653.

Carlessi, L., Fusar Poli, E., De Filippis, L., Delia, D., 2013. ATM-deficient human neural stem cells as an in vitro model system to study neurodegeneration. DNA Repair 12 (8), 605–611. https://doi.org/10.1016/j.dnarep.2013.04.013.

Carlessi, L., Fusar Poli, E., Bechi, G., et al., 2014. Functional and molecular defects of hiPSC-derived neurons from patients with ATM deficiency. Cell Death Dis. 5, e1342 https://doi.org/10.1038/cddis.2014.310.

Chandra, T., Narita, M., 2013. High-order chromatin structure and the epigenome in SAHFs. Nucleus 4 (1), 23–28. https://doi.org/10.4161/nucl.23189.

Chatterjee, N., Walker, G.C., 2017a. Mechanisms of DNA damage, repair, and mutagenesis. Environ. Mol. Mutagen 58 (5), 235–263. https://doi.org/10.1002/em.22087.
Chatterjee, N., Walker, G.C., 2017b. Mechanisms of DNA damage, repair, and mutagenesis. Environ. Mol. Mutagen. https://doi.org/10.1002/em.22087. May 09.
Chen, C.W., Buj, R., Dahl, E.S., Leon, K.E., Aird, K.M., 2020b. ATM inhibition synergizes with fenofibrate in high grade serous ovarian cancer cells. Heliyon 6 (9), e05097. https://doi.org/10.1016/j.heliyon.2020.e05097.
Chen, G., Kroemer, G., Kepp, O., 2020a. Mitophagy: an emerging role in aging and age-associated diseases. Front Cell Dev. Biol. 8, 200. https://doi.org/10.3389/fcell.2020.00200.
Chen, P., Peng, C., Luff, J., et al., 2003. Oxidative stress is responsible for deficient survival and dendritogenesis in purkinje neurons from ataxia-telangiectasia mutated mutant mice. Research Support, Non-U.S. Gov't. J. Neurosci. 23 (36), 11453–11460.
Cheng, A., Tse, K.H., Chow, H.M., et al., 2020. ATM loss disrupts the autophagy-lysosomal pathway. Autophagy 1–13. https://doi.org/10.1080/15548627.2020.1805860.
Chow, H.M., Cheng, A., Song, X., Swerdel, M.R., Hart, R.P., Herrup, K., 2019. ATM is activated by ATP depletion and modulates mitochondrial function through NRF1. J. Cell Biol. 218 (3), 909–928. https://doi.org/10.1083/jcb.201806197.
Colombo, C.V., Gnugnoli, M., Gobbini, E., Longhese, M.P., 2020. How do cells sense DNA lesions? Biochem Soc. Trans. 48 (2), 677–691. https://doi.org/10.1042/BST20191118.
Coppe, J.P., Desprez, P.Y., Krtolica, A., Campisi, J., 2010. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev. Pathol. 5, 99–118. https://doi.org/10.1146/annurev-pathol-121808-102144.
Cosentino, C., Grieco, D., Costanzo, V., 2011. ATM activates the pentose phosphate pathway promoting anti-oxidant defence and DNA repair. EMBO J. 30 (3), 546–555. https://doi.org/10.1038/emboj.2010.330.
Coufal, N.G., Garcia-Perez, J.L., Peng, G.E., et al., 2011. Ataxia telangiectasia mutated (ATM) modulates long interspersed element-1 (L1) retrotransposition in human neural stem cells. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. Proc. Natl. Acad. Sci. USA 108 (51). https://doi.org/10.1073/pnas.1100273108.
Crawford, T.O., Skolasky, R.L., Fernandez, R., Rosquist, K.J., Lederman, H.M., 2006. Survival probability in ataxia telangiectasia. Arch. Dis. Child 91 (7), 610–611. https://doi.org/10.1136/adc.2006.094268.
d'Adda di Fagagna, F., Reaper, P.M., Clay-Farrace, L., et al., 2003. A DNA damage checkpoint response in telomere-initiated senescence. Nature 426 (6963), 194–198. https://doi.org/10.1038/nature02118.
Dai, J., Huang, Y.J., He, X., et al., 2019. Acetylation blocks cGAS activity and inhibits self-DNA-induced autoimmunity. Cell 176 (6), 1447–1460. https://doi.org/10.1016/j.cell.2019.01.016.
Dar, I., Yosha, G., Elfassy, R., et al., 2011. Investigation of the functional link between ATM and NBS1 in the DNA damage response in the mouse cerebellum. J. Biol. Chem. 286 (17), 15361–15376. https://doi.org/10.1074/jbc.M110.204172.
D'Assante, R., Fusco, A., Palamaro, L., et al., 2017. Abnormal cell-clearance and accumulation of autophagic vesicles in lymphocytes from patients affected with Ataxia-Teleangiectasia. Clin. Immunol. 175, 16–25. https://doi.org/10.1016/j.clim.2016.11.015.
Davis, T., Kipling, D., 2009. Assessing the role of stress signalling via p38 MAP kinase in the premature senescence of ataxia telangiectasia and Werner syndrome fibroblasts. Biogerontology 10 (3), 253–266. https://doi.org/10.1007/s10522-008-9179-x.
Day, K., Waite, L.L., Thalacker-Mercer, A., et al., 2013. Differential DNA methylation with age displays both common and dynamic features across human tissues that are influenced by CpG landscape. Genome Biol. 14 (9), R102. https://doi.org/10.1186/gb-2013-14-9-r102.
De Cecco, M., Ito, T., Petrashen, A.P., et al., 2019. L1 drives IFN in senescent cells and promotes age-associated inflammation (Feb). Nature 566 (7742), 73–78. https://doi.org/10.1038/s41586-018-0784-9.
Di Micco, R., Krizhanovsky, V., Baker, D., d'Adda di Fagagna, F., 2020. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat. Rev. Mol. Cell Biol. https://doi.org/10.1038/s41580-020-00314-w. Dec 16.
Di Micco, R., Krizhanovsky, V., Baker, D., d'Adda di Fagagna, F., 2021. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat. Rev. Mol. Cell Biol. 22 (2), 75–95. https://doi.org/10.1038/s41580-020-00314-w.
Djeghloul, D., Kuranda, K., Kuzniak, I., et al., 2016. Age-associated decrease of the histone methyltransferase SUV39H1 in HSC perturbs heterochromatin and B lymphoid differentiation. Stem Cell Rep. 6 (6), 970–984. https://doi.org/10.1016/j.stemcr.2016.05.007.
Donath, H., Hess, U., Kieslich, M., et al., 2020. Diabetes in Patients With Ataxia Telangiectasia: A National Cohort Study. Front Pedia 8, 317. https://doi.org/10.3389/fped.2020.00317.
Dou, Z., Xu, C., Donahue, G., et al., 2015. Autophagy mediates degradation of nuclear lamina. Nature 527 (7576), 105–109. https://doi.org/10.1038/nature15548.
Dou, Z., Ghosh, K., Vizioli, M.G., et al., 2017. Cytoplasmic chromatin triggers inflammation in senescence and cancer. Nature 550 (7676), 402–406. https://doi.org/10.1038/nature24050.
D'Souza, A.D., Parish, I.A., Krause, D.S., Kaech, S.M., Shadel, G.S., 2013. Reducing mitochondrial ROS improves disease-related pathology in a mouse model of ataxia-telangiectasia. Mol. Ther. 21 (1), 42–48. https://doi.org/10.1038/mt.2012.203.
Ermolaeva, M., Neri, F., Ori, A., Rudolph, K.L., 2018. Cellular and epigenetic drivers of stem cell ageing. Nat. Rev. Mol. Cell Biol. 19 (9), 594–610. https://doi.org/10.1038/s41580-018-0020-3.
Erttmann, S.F., Hartlova, A., Sloniecka, M., et al., 2016. Loss of the DNA damage repair kinase ATM impairs inflammasome-dependent anti-bacterial innate immunity. Immunity 45 (1), 106–118. https://doi.org/10.1016/j.immuni.2016.06.018.
Fafian-Labora, J.A., O'Loghlen, A., 2020. Classical and nonclassical intercellular communication in senescence and ageing. Trends Cell Biol. 30 (8), 628–639. https://doi.org/10.1016/j.tcb.2020.05.003.
Fang, E.F., Kassahun, H., Croteau, D.L., et al., 2016. NAD(+) replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair. Cell Metab. 24 (4), 566–581. https://doi.org/10.1016/j.cmet.2016.09.004.
Fernandez, A.M., Carro, E.M., Lopez-Lopez, C., Torres-Aleman, I., 2005. Insulin-like growth factor I treatment for cerebellar ataxia: addressing a common pathway in the pathological cascade? Brain Res. Brain Res. Rev. 50 (1), 134–141. https://doi.org/10.1016/j.brainresrev.2005.05.003.
Fernandez-Marcos, P.J., Nobrega-Pereira, S., 2016. NADPH: new oxygen for the ROS theory of aging. Oncotarget 7 (32), 50814–50815. https://doi.org/10.18632/oncotarget.10744.
Fortuny, A., Polo, S.E., 2018. The response to DNA damage in heterochromatin domains. Chromosoma 127 (3), 291–300. https://doi.org/10.1007/s00412-018-0669-6.
Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat. Rev. Endocrinol. 14 (10), 576–590. https://doi.org/10.1038/s41574-018-0059-4.
Fumagalli, M., Rossiello, F., Clerici, M., et al., 2012. Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. Research Support, N.I.H., Extramural Research Supportt, Non-U.S. Gov't. Nat. Cell Biol. 14 (4), 355–365. https://doi.org/10.1038/ncb2466.
Gil, J., 2019. Cellular senescence causes ageing. Nat. Rev. Mol. Cell Biol. 20 (7), 388. https://doi.org/10.1038/s41580-019-0128-0.
Gluck, S., Guey, B., Gulen, M.F., et al., 2017. Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence. Nat. Cell Biol. 19 (9), 1061–1070. https://doi.org/10.1038/ncb3586.
Goldstein, M., Kastan, M.B., 2015. The DNA damage response: implications for tumor responses to radiation and chemotherapy. Annu Rev. Med 66, 129–143. https://doi.org/10.1146/annurev-med-081313-121208.
Gorbunova, V., Seluanov, A., Mita, P., et al., 2021. The role of retrotransposable elements in ageing and age-associated diseases. Nature 596 (7870), 43–53. https://doi.org/10.1038/s41586-021-03542-y.
Gorgoulis, V., Adams, P.D., Alimonti, A., et al., 2019. Cellular senescence: defining a path forward. Cell 179 (4), 813–827. https://doi.org/10.1016/j.cell.2019.10.005.
Grattarola, M., Spaggiari, S., Chessa, L., Savio, C., Nicolini, C., Vergani, L., 2003. A structural characterization of in situ chromatin on cell lines isolated from patients affected by ataxia telangiectasia. Int J. Biol. Macromol. 33 (1–3), 23–29. https://doi.org/10.1016/s0141-8130(03)00060-6.
Griffith, J.D., Comeau, L., Rosenfield, S., et al., 1999. Mammalian telomeres end in a large duplex loop. Cell 97 (4), 503–514.
Guo, Z., Kozlov, S., Lavin, M.F., Person, M.D., Paull, T.T., 2010a. ATM activation by oxidative stress. Science 330 (6003), 517–521. https://doi.org/10.1126/science.1192912.
Guo, Z., Deshpande, R., Paull, T.T., 2010b. ATM activation in the presence of oxidative stress. Cell Cycle 9 (24), 4805–4811. https://doi.org/10.4161/cc.9.24.14323.
Gupte, R., Liu, Z., Kraus, W.L., 2017. PARPs and ADP-ribosylation: recent advances linking molecular functions to biological outcomes. Genes Dev. 31 (2), 101–126. https://doi.org/10.1101/gad.291518.116.
Haag, S.M., Gulen, M.F., Reymond, L., et al., 2018. Targeting STING with covalent small-molecule inhibitors. Nature 559 (7713), 269–273. https://doi.org/10.1038/s41586-018-0287-8.
Hanawalt, P., Sweasy, J., 2020. Mechanistic understanding of cellular responses to genomic stress. Environ. Mol. Mutagen 61 (1), 25–33. https://doi.org/10.1002/em.22349.
Hartlova, A., Erttmann, S.F., Raffi, F.A., et al., 2015. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. Immunity 42 (2), 332–343. https://doi.org/10.1016/j.immuni.2015.01.012.
Hayflick, L., 1965. The Limited in Vitro Lifetime of Human Diploid Cell Strains. Exp. Cell Res 37, 614–636.
Hernandez-Segura, A., Nehme, J., Demaria, M., 2018. Hallmarks of cellular senescence. Trends Cell Biol. 28 (6), 436–453. https://doi.org/10.1016/j.tcb.2018.02.001.
Herranz, D., Munoz-Martin, M., Canamero, M., et al., 2010. Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. Nat. Commun. 1, 3. https://doi.org/10.1038/ncomms1001.
Hipp, M.S., Kasturi, P., Hartl, F.U., 2019. The proteostasis network and its decline in ageing. Nat. Rev. Mol. Cell Biol. 20 (7), 421–435. https://doi.org/10.1038/s41580-019-0101-y.
Hishiya, A., Ito, M., Aburatani, H., Motoyama, N., Ikeda, K., Watanabe, K., 2005. Ataxia telangiectasia mutated (Atm) knockout mice as a model of osteopenia due to impairedbone formation. Research Support, Non-U.S. Gov't. Bone 37 (4), 497–503. https://doi.org/10.1016/j.bone.2005.05.012.
Ho, S.S., Zhang, W.Y., Tan, N.Y., et al., 2016. The DNA structure-specific endonuclease MUS81 Mediates DNA sensor STING-dependent host rejection of prostate cancer cells. Immunity 44 (5), 1177–1189. https://doi.org/10.1016/j.immuni.2016.04.010.
Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biol. 14 (10), R115. https://doi.org/10.1186/gb-2013-14-10-r115.
Horvath, S., Raj, K., 2018. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat. Rev. Genet 19 (6), 371–384. https://doi.org/10.1038/s41576-018-0004-3.

Hotokezaka, Y., Katayama, I., Nakamura, T., 2020. ATM-associated signalling triggers the unfolded protein response and cell death in response to stress. Commun. Biol. 3 (1), 378. https://doi.org/10.1038/s42003-020-1102-2.
Houtkooper, R.H., Canto, C., Wanders, R.J., Auwerx, J., 2010. The secret life of NAD+: an old metabolite controlling new metabolic signaling pathways. Endocr. Rev. 31 (2), 194–223. https://doi.org/10.1210/er.2009-0026.
Hui, C.W., Song, X., Ma, F., Shen, X., Herrup, K., 2018. Ibuprofen prevents progression of ataxia telangiectasia symptoms in ATM-deficient mice. J. Neuroinflamm. 15 (1), 308. https://doi.org/10.1186/s12974-018-1338-7.
Imai, S.I., Guarente, L., 2016. It takes two to tango: NAD(+) and sirtuins in aging/longevity control. NPJ Aging Mech. Dis. 2, 16017. https://doi.org/10.1038/npjamd.2016.17.
Ishikawa, H., Barber, G.N., 2008. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature 455 (7213), 674–678. https://doi.org/10.1038/nature07317.
Ishikawa, H., Ma, Z., Barber, G.N., 2009. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature 461 (7265), 788–792. https://doi.org/10.1038/nature08476.
Ito, K., Hirao, A., Arai, F., et al., 2004. Regulation of oxidative stress by ATM is required for self-renewal of haematopoietic stem cells. Nature 431 (7011), 997–1002. https://doi.org/10.1038/nature02989.
Ito, K., Takubo, K., Arai, F., et al., 2007. Regulation of reactive oxygen species by Atm is essential for proper response to DNA double-strand breaks in lymphocytes. Research Support, Non-U.S. Gov't. J. Immunol. 178 (1), 103–110.
Ivanov, A., Pawlikowski, J., Manoharan, I., et al., 2013. Lysosome-mediated processing of chromatin in senescence. J. Cell Biol. 202 (1), 129–143. https://doi.org/10.1083/jcb.201212110.
Jackson, S.P., Bartek, J., 2009. The DNA-damage response in human biology and disease. Nature 461 (7267), 1071–1078. https://doi.org/10.1038/nature08467.
Jacob-Hirsch, J., Eyal, E., Knisbacher, B.A., et al., 2018. Whole-genome sequencing reveals principles of brain retrotransposition in neurodevelopmental disorders. Cell Res 28 (2), 187–203. https://doi.org/10.1038/cr.2018.8.
Jiang, D., Zhang, Y., Hart, R.P., Chen, J., Herrup, K., Li, J., 2015. Alteration in 5-hydroxymethylcytosine-mediated epigenetic regulation leads to Purkinje cell vulnerability in ATM deficiency. Brain 138 (Pt 12), 3520–3536. https://doi.org/10.1093/brain/awv284.
Jimeno, S., Mejias-Navarro, F., Prados-Carvajal, R., Huertas, P., 2019. Controlling the balance between chromosome break repair pathways. Adv. Protein Chem. Struct. Biol. 115, 95–134. https://doi.org/10.1016/bs.apcsb.2018.10.004.
Jin, S., Cordes, N., 2019. ATM controls DNA repair and mitochondria transfer between neighboring cells. Cell Commun. Signal 17 (1), 144. https://doi.org/10.1186/s12964-019-0472-x.
Junnila, R.K., List, E.O., Berryman, D.E., Murrey, J.W., Kopchick, J.J., 2013. The GH/IGF-1 axis in ageing and longevity. Nat. Rev. Endocrinol. 9 (6), 366–376. https://doi.org/10.1038/nrendo.2013.67.
Kamsler, A., Daily, D., Hochman, A., et al., 2001. Increased oxidative stress in ataxia telangiectasia evidenced by alterations in redox state of brains from Atm-deficient mice. Cancer Res 61 (5), 1849–1854.
Kanatsu-Shinohara, M., Yamamoto, T., Toh, H., et al., 2019. Aging of spermatogonial stem cells by Jnk-mediated glycolysis activation. Proc. Natl. Acad. Sci. USA 116 (33), 16404–16409. https://doi.org/10.1073/pnas.1904980116.
Kane, A.E., Sinclair, D.A., 2019. Epigenetic changes during aging and their reprogramming potential. Crit. Rev. Biochem Mol. Biol. 54 (1), 61–83. https://doi.org/10.1080/10409238.2019.1570075.
Kang, H.T., Park, J.T., Choi, K., et al., 2017. Chemical screening identifies ATM as a target for alleviating senescence. Nat. Chem. Biol. 13 (6), 616–623. https://doi.org/10.1038/nchembio.2342.
Katzir, I., Adler, M., Karin, O., Mendelsohn-Cohen, N., Mayo, A., Alon, U., 2021. Senescent cells and the incidence of age-related diseases. Aging Cell 20 (3), e13314. https://doi.org/10.1111/acel.13314.
Khan, S.S., Shah, S.J., Klyachko, E., et al., 2017. A null mutation in SERPINE1 protects against biological aging in humans. Sci. Adv. 3 (11) https://doi.org/10.1126/sciadv.aao1617.
Khoronenkova, S.V., 2016. Mechanisms of non-canonical activation of ataxia telangiectasia mutated. Biochem. (Mosc.) 81 (13), 1669–1675. https://doi.org/10.1134/S0006297916130058.
Khosla, S., Farr, J.N., Tchkonia, T., Kirkland, J.L., 2020. The role of cellular senescence in ageing and endocrine disease. Nat. Rev. Endocrinol. https://doi.org/10.1038/s41574-020-0335-y.
Kim, J., Wong, P.K., 2009. Oxidative stress is linked to ERK1/2-p16 signaling-mediated growth defect in ATM-deficient astrocytes. Research Support, Non-U.S. Gov't. J. Biol. Chem. 284 (21), 14396–14404. https://doi.org/10.1074/jbc.M808116200.
Klaips, C.L., Jayaraj, G.G., Hartl, F.U., 2018. Pathways of cellular proteostasis in aging and disease. J. Cell Biol. 217 (1), 51–63. https://doi.org/10.1083/jcb.201709072.
Kojis, T.L., Gatti, R.A., Sparkes, R.S., 1991. The cytogenetics of ataxia telangiectasia. Cancer Genet. Cytogenet. 56 (2), 143–156.
Kozlov, S.V., Waardenberg, A.J., Engholm-Keller, K., Arthur, J.W., Graham, M.E., Lavin, M.F., 2015. ROS-activated ATM-dependent phosphorylation of cytoplasmic substrates identified by large scale phosphoproteomics screen. Mol. Cell Proteom. https://doi.org/10.1074/mcp.M115.055723. Dec 23.
Kozlov, S.V., Waardenberg, A.J., Engholm-Keller, K., Arthur, J.W., Graham, M.E., Lavin, M., 2016. Reactive oxygen species (ROS)-activated ATM-dependent phosphorylation of cytoplasmic substrates identified by large-scale phosphoproteomics screen. Mol. Cell Proteom. 15 (3), 1032–1047. https://doi.org/10.1074/mcp.M115.055723.
Labbadia, J., Morimoto, R.I., 2015. The biology of proteostasis in aging and disease. Annu Rev. Biochem. 84, 435–464. https://doi.org/10.1146/annurev-biochem-060614-033955.
Lan, Y.Y., Heather, J.M., Eisenhaure, T., et al., 2019. Extranuclear DNA accumulates in aged cells and contributes to senescence and inflammation. Aging Cell 18 (2), e12901. https://doi.org/10.1111/acel.12901.
Lee, J.H., Paull, T.T., 2020. Mitochondria at the crossroads of ATM-mediated stress signaling and regulation of reactive oxygen species. Mar 21 Redox Biol. 32, 101511. https://doi.org/10.1016/j.redox.2020.101511.
Lee, J.H., Mand, M.R., Kao, C.H., et al., 2018. ATM directs DNA damage responses and proteostasis via genetically separable pathways. Sci. Signal 11 (512). https://doi.org/10.1126/scisignal.aan5598.
Lee, J.H., Ryu, S.W., Ender, N.A., Paull, T.T., 2021. Poly-ADP-ribosylation drives loss of protein homeostasis in ATM and Mre11 deficiency. Mol. Cell 81 (7), 1515–1533. https://doi.org/10.1016/j.molcel.2021.01.019.
Lee, S.S., Bohrson, C., Pike, A.M., Wheelan, S.J., Greider, C.W., 2015. ATM kinase is required for telomere elongation in mouse and human cells. Cell Rep. 13 (8), 1623–1632. https://doi.org/10.1016/j.celrep.2015.10.035.
Li, J., Chen, J., Ricupero, C.L., et al., 2012. Nuclear accumulation of HDAC4 in ATM deficiency promotes neurodegeneration in ataxia telangiectasia. Nat. Med 18 (5), 783–790. https://doi.org/10.1038/nm.2709.
Likhatcheva, M., Gieling, R.G., Brown, J.A.L., Demonacos, C., Williams, K.J., 2021. A novel mechanism of ataxia telangiectasia mutated mediated regulation of chromatin remodeling in hypoxic conditions. Front Cell Dev. Biol. 9, 720194 https://doi.org/10.3389/fcell.2021.720194.
Lipinski, M.M., Hoffman, G., Ng, A., et al., 2010. A genome-wide siRNA screen reveals multiple mTORC1 independent signaling pathways regulating autophagy under normal nutritional conditions. Dev. Cell 18 (6), 1041–1052. https://doi.org/10.1016/j.devcel.2010.05.005.
Liu, D., Gao, Y., Liu, J., et al., 2021. Intercellular mitochondrial transfer as a means of tissue revitalization. Signal Transduct. Target Ther. 6 (1), 65. https://doi.org/10.1038/s41392-020-00440-z.
Liu, G.Y., Sabatini, D.M., 2020. mTOR at the nexus of nutrition, growth, ageing and disease. Nat. Rev. Mol. Cell Biol. 21 (4), 183–203. https://doi.org/10.1038/s41580-019-0199-y.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153 (6), 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039.
Luo, X., Suzuki, M., Ghandhi, S.A., Amundson, S.A., Boothman, D.A., 2014. ATM regulates insulin-like growth factor 1-secretory clusterin (IGF-1-sCLU) expression that protects cells against senescence. PLoS One 9 (6), e99983. https://doi.org/10.1371/journal.pone.0099983.
Martinez-Cue, C., Rueda, N., 2020. Cellular senescence in neurodegenerative diseases. Front. Cell Neurosci. 14, 16. https://doi.org/10.3389/fncel.2020.00016.
Matei, I.R., Gladdy, R.A., Nutter, L.M., Canty, A., Guidos, C.J., Danska, J.S., 2007. ATM deficiency disrupts Tcra locus integrity and the maturation of CD4+CD8+ thymocytes. Research Support, Non-U.S. Gov't. Blood 109 (5), 1887–1896. https://doi.org/10.1182/blood-2006-05-020917.
Matsuoka, S., Ballif, B.A., Smogorzewska, A., et al., 2007. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science 316 (5828), 1160–1166. https://doi.org/10.1126/science.1140321.
Maxwell, P.H., Burhans, W.C., Curcio, M.J., 2011. Retrotransposition is associated with genome instability during chronological aging. Proc. Natl. Acad. Sci. USA 108 (51), 20376–20381. https://doi.org/10.1073/pnas.1100271108.
McGrath-Morrow, S.A., Ndeh, R., Collaco, J.M., et al., 2018. Inflammation and transcriptional responses of peripheral blood mononuclear cells in classic ataxia telangiectasia. PLoS One 13 (12), e0209496. https://doi.org/10.1371/journal.pone.0209496.
McGrath-Morrow, S.A., Ndeh, R., Helmin, K.A., et al., 2020. DNA methylation and gene expression signatures are associated with ataxia-telangiectasia phenotype. Sci. Rep. 10 (1), 7479. https://doi.org/10.1038/s41598-020-64514-2.
Metcalfe, J.A., Parkhill, J., Campbell, L., et al., 1996. Accelerated telomere shortening in ataxia telangiectasia. Nat. Genet 13 (3), 350–353. https://doi.org/10.1038/ng0796-350.
Michelini, F., Jalihal, A.P., Francia, S., et al., 2018. From "Cellular" RNA to "Smart" RNA: multiple roles of RNA in genome stability and beyond. Chem. Rev. 118 (8), 4365–4403. https://doi.org/10.1021/acs.chemrev.7b00487.
Miller, K.N., Victorelli, S.G., Salmonowicz, H., et al., 2021. Cytoplasmic DNA: sources, sensing, and role in aging and disease. Cell 184 (22), 5506–5526. https://doi.org/10.1016/j.cell.2021.09.034.
Morgan, J.L., Holcomb, T.M., Morrissey, R.W., 1968. Radiation reaction in ataxia telangiectasia. Am. J. Dis. Child 116 (5), 557–558. https://doi.org/10.1001/archpedi.1968.02100020561022.
Naka, K., Tachibana, A., Ikeda, K., Motoyama, N., 2004. Stress-induced premature senescence in hTERT-expressing ataxia telangiectasia fibroblasts. J. Biol. Chem. 279 (3), 2030–2037. https://doi.org/10.1074/jbc.M309457200.
Narita, M., Nunez, S., Heard, E., et al., 2003. Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. Cell 113 (6), 703–716.
Nayler, S.P., Powell, J.E., Vanichkina, D.P., et al., 2017. Human iPSC-derived cerebellar neurons from a patient with ataxia-telangiectasia reveal disrupted gene regulatory networks. Front. Cell Neurosci. 11, 321. https://doi.org/10.3389/fncel.2017.00321.
Nguyen, Q., Aguado, J., Iannelli, F., et al., 2018. Target-enrichment sequencing for detailed characterization of small RNAs. Nat. Protoc. 13 (4), 768–786. https://doi.org/10.1038/nprot.2018.001.
Nissenkorn, A., Ben-Zeev, B., 2015. Ataxia telangiectasia. Handb. Clin. Neurol. 132, 199–214. https://doi.org/10.1016/B978-0-444-62702-5.00014-7.

Nissenkorn, A., Levy-Shraga, Y., Banet-Levi, Y., Lahad, A., Sarouk, I., Modan-Moses, D., 2016. Endocrine abnormalities in ataxia telangiectasia: findings from a national cohort. Pedia Res 79 (6), 889–894. https://doi.org/10.1038/pr.2016.19.
Onn L., Portillo M., Ilic S., et al. SIRT6 is a DNA double-strand break sensor. Elife. Jan 29 2020;9doi:10.7554/eLife.51636.
O'Sullivan, R.J., Karlseder, J., 2010. Telomeres: protecting chromosomes against genome instability. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't ⃠Review. Nat. Rev. Mol. Cell Biol. 11 (3), 171–181. https://doi.org/10.1038/nrm2848.
O'Sullivan, R.J., Kubicek, S., Schreiber, S.L., Karlseder, J., 2010. Reduced histone biosynthesis and chromatin changes arising from a damage signal at telomeres. Nat. Struct. Mol. Biol. 17 (10), 1218–1225. https://doi.org/10.1038/nsmb.1897.
Ozcelik, A.A., Perk, P., Bay, A., Erbagci, B., Gok, A., Demircioglu Kılıc, B., 2017. The predictive role of heat shock protein 27–60 levels in pediatric patients with ataxia telangiectasia. Eur. J. Paediatr. Neurol. 21, e215 https://doi.org/10.1016/j.ejpn.2017.04.1119.
Park, J., Jo, Y.H., Cho, C.H., et al., 2013. ATM-deficient human fibroblast cells are resistant to low levels of DNA double-strand break induced apoptosis and subsequently undergo drug-induced premature senescence. Biochem. Biophys. Res. Commun. 430 (1), 429–435. https://doi.org/10.1016/j.bbrc.2012.11.040.
Paull, T.T., 2015. Mechanisms of ATM activation. Annu Rev. Biochem 84, 711–738. https://doi.org/10.1146/annurev-biochem-060614-034335.
Perlman, S.L., Boder Deceased, E., Sedgewick, R.P., Gatti, R.A.Ataxia-telangiectasia, 2012. Handb. Clin. Neurol. 103, 307–332. https://doi.org/10.1016/B978-0-444-51892-7.00019-X.
Petr, M.A., Tulika, T., Carmona-Marin, L.M., Scheibye-Knudsen, M., 2020. Protecting the aging genome. Trends Cell Biol. https://doi.org/10.1016/j.tcb.2019.12.001. Jan 6.
Poletto, M., Yang, D., Fletcher, S.C., et al., 2017. Modulation of proteostasis counteracts oxidative stress and affects DNA base excision repair capacity in ATM-deficient cells. Nucleic Acids Res 45 (17), 10042–10055. https://doi.org/10.1093/nar/gkx635.
Post, Y., Clevers, H., 2019. Defining adult stem cell function at its simplest: the ability to replace lost cells through mitosis. Cell Stem Cell 25 (2), 174–183. https://doi.org/10.1016/j.stem.2019.07.002.
Qi, Y., Qiu, Q., Gu, X., Tian, Y., Zhang, Y., 2016. ATM mediates spermidine-induced mitophagy via PINK1 and Parkin regulation in human fibroblasts. Sci. Rep. 6, 24700. https://doi.org/10.1038/srep24700.
Qian, M., Liu, Z., Peng, L., et al., 2018. Boosting ATM activity alleviates aging and extends lifespan in a mouse model of progeria. Elife 7. https://doi.org/10.7554/eLife.34836.
Quek, H., Luff, J., Cheung, K., et al., 2017. A rat model of ataxia-telangiectasia: evidence for a neurodegenerative phenotype. Hum. Mol. Genet. 26 (1), 109–123. https://doi.org/10.1093/hmg/ddw371.
Quick, K.L., Dugan, L.L., 2001. Superoxide stress identifies neurons at risk in a model of ataxia-telangiectasia. Research Support, Non-U.S. Gov't. Ann. Neurol. 49 (5), 627–635.
Rajman, L., Chwalek, K., Sinclair, D.A., 2018. Therapeutic Potential of NAD-Boosting Molecules: The In Vivo Evidence. Mar 6 Cell Metab. 27 (3), 529–547. https://doi.org/10.1016/j.cmet.2018.02.011.
Reichenbach, J., Schubert, R., Schindler, D., Muller, K., Bohles, H., Zielen, S., 2002. Elevated oxidative stress in patients with ataxia telangiectasia. Research Support, Non-U.S. Gov't. Antioxid. Redox Signal. 4 (3), 465–469. https://doi.org/10.1089/15230860260196254.
Ren, X., Zou, L., Zhang, X., et al., 2017. Redox signaling mediated by thioredoxin and glutathione systems in the central nervous system. Antioxid. Redox Signal 27 (13), 989–1010. https://doi.org/10.1089/ars.2016.6925.
Ribezzo, F., Shiloh, Y., Schumacher, B., 2016. Systemic DNA damage responses in aging and diseases. Semin Cancer Biol. https://doi.org/10.1016/j.semcancer.2015.12.005. Jan 7.
Risques, R.A., Kennedy, S.R., 2018. Aging and the rise of somatic cancer-associated mutations in normal tissues. PLoS Genet 14 (1), e1007108. https://doi.org/10.1371/journal.pgen.1007108.
Rodgers, J.T., Lerin, C., Haas, W., Gygi, S.P., Spiegelman, B.M., Puigserver, P., 2005. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. Nature 434 (7029), 113–118. https://doi.org/10.1038/nature03354.
Rodier, F., Campisi, J., 2011. Four faces of cellular senescence. J. Cell Biol. 192 (4), 547–556. https://doi.org/10.1083/jcb.201009094.
Rossiello, F., Aguado, J., Sepe, S., et al., 2017. DNA damage response inhibition at dysfunctional telomeres by modulation of telomeric DNA damage response RNAs. Nat. Commun. 8, 13980. https://doi.org/10.1038/ncomms13980.
Rothblum-Oviatt, C., Wright, J., Lefton-Greif, M.A., McGrath-Morrow, S.A., Crawford, T. O., Lederman, H.M., 2016. Ataxia telangiectasia: a review. Orphanet J. Rare Dis. 11 (1), 159. https://doi.org/10.1186/s13023-016-0543-7.
Rotman, G., Shiloh, Y., 1997. Ataxia-telangiectasia: is ATM a sensor of oxidative damage and stress? Bioessays 19 (10), 911–917. https://doi.org/10.1002/bies.950191011.
Sabath, N., Levy-Adam, F., Younis, A., et al., 2020. Cellular proteostasis decline in human senescence. Proc. Natl. Acad. Sci. USA 117 (50), 31902–31913. https://doi.org/10.1073/pnas.2018138117.
Saksouk, N., Simboeck, E., Dejardin, J., 2015. Constitutive heterochromatin formation and transcription in mammals. Epigen. Chrom. 8, 3. https://doi.org/10.1186/1756-8935-8-3.
Schlam-Babayov, S., Bensimon, A., Harel, M., et al., 2021. Phosphoproteomics reveals novel modes of function and inter-relationships among PIKKs in response to genotoxic stress. EMBO J. 40 (2), e104400 https://doi.org/10.15252/embj.2020104400.
Schneider, J.G., Finck, B.N., Ren, J., et al., 2006. ATM-dependent suppression of stress signaling reduces vascular disease in metabolic syndrome. Cell Metab. 4 (5), 377–389. https://doi.org/10.1016/j.cmet.2006.10.002.
Schubert, R., Reichenbach, J., Zielen, S., 2005. Growth factor deficiency in patients with ataxia telangiectasia. Clin. Exp. Immunol. 140 (3), 517–519. https://doi.org/10.1111/j.1365-2249.2005.02782.x.
Schumacher, B., Pothof, J., Vijg, J., Hoeijmakers, J.H.J., 2021. The central role of DNA damage in the ageing process (Apr). Nature 592 (7856), 695–703. https://doi.org/10.1038/s41586-021-03307-7.
Sedivy, J.M., Banumathy, G., Adams, P.D., 2008. Aging by epigenetics–a consequence of chromatin damage? Exp. Cell Res 314 (9), 1909–1917. https://doi.org/10.1016/j.yexcr.2008.02.023.
Sen, P., Shah, P.P., Nativio, R., Berger, S.L., 2016. Epigenetic mechanisms of longevity and aging. Cell 166 (4), 822–839. https://doi.org/10.1016/j.cell.2016.07.050.
Shahrabani-Gargir, L., Pandita, T.K., Werner, H., 2004. Ataxia-telangiectasia mutated gene controls insulin-like growth factor I receptor gene expression in a deoxyribonucleic acid damage response pathway via mechanisms involving zinc-finger transcription factors Sp1 and WT1. Endocrinology 145 (12), 5679–5687. https://doi.org/10.1210/en.2004-0613.
Shiloh, Y., 2014. ATM: expanding roles as a chief guardian of genome stability. Exp. Cell Res 329 (1), 154–161. https://doi.org/10.1016/j.yexcr.2014.09.002.
Shiloh, Y., 2020. The cerebellar degeneration in ataxia-telangiectasia: a case for genome instability. DNA Repair 95, 102950. https://doi.org/10.1016/j.dnarep.2020.102950.
Shiloh, Y., Ziv, Y., 2013. The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. Nat. Rev. Mol. Cell Biol. 14 (4), 197–210.
Shiloh, Y., Tabor, E., Becker, Y., 1982. Colony-forming ability of ataxia-telangiectasia skin fibroblasts is an indicator of their early senescence and increased demand for growth factors. Exp. Cell Res 140 (1), 191–199. https://doi.org/10.1016/0014-4827(82)90169-0.
Shiloh, Y., Tabor, E., Becker, Y., 1983. Abnormal response of ataxia-telangiectasia cells to agents that break the deoxyribose moiety of DNA via a targeted free radical mechanism. Carcinogenesis 4 (10), 1317–1322. https://doi.org/10.1093/carcin/4.10.1317.
Shiloh, Y., Lederman, H.M., Ataxia-telangiectasia, A.-T., 2017. An emerging dimension of premature ageing. Ageing Res Rev. 33, 76–88. https://doi.org/10.1016/j.arr.2016.05.002.
Sies, H., Jones, D.P., 2020. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nat. Rev. Mol. Cell Biol. 21 (7), 363–383. https://doi.org/10.1038/s41580-020-0230-3.
Sitte, N., Huber, M., Grune, T., et al., 2000. Proteasome inhibition by lipofuscin/ceroid during postmitotic aging of fibroblasts. FASEB J. 14 (11), 1490–1498. https://doi.org/10.1096/fj.14.11.1490.
Smilenov, L.B., Morgan, S.E., Mellado, W., Sawant, S.G., Kastan, M.B., Pandita, T.K., 1997. Influence of ATM function on telomere metabolism. Oncogene 15 (22), 2659–2665. https://doi.org/10.1038/sj.onc.1201449.
Song, X., Ma, F., Herrup, K., 2019. Accumulation of cytoplasmic DNA Due to ATM deficiency activates the microglial viral response system with neurotoxic consequences. J. Neurosci. 39 (32), 6378–6394. https://doi.org/10.1523/JNEUROSCI.0774-19.2019.
Stagni, V., Cirotti, C., Barila, D., 2018. Ataxia-telangiectasia mutated kinase in the control of oxidative stress, mitochondria, and autophagy in cancer: a maestro with a large orchestra. Front Oncol. 8, 73. https://doi.org/10.3389/fonc.2018.00073.
Stern, N., Hochman, A., Zemach, N., et al., 2002. Accumulation of DNA damage and reduced levels of nicotine adenine dinucleotide in the brains of Atm-deficient mice. J. Biol. Chem. 277 (1), 602–608. https://doi.org/10.1074/jbc.M106798200.
Suarez, F., Mahlaoui, N., Canioni, D., et al., 2015. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. J. Clin. Oncol. 33 (2), 202–208. https://doi.org/10.1200/JCO.2014.56.5101.
Sun, N., Youle, R.J., Finkel, T., 2016. The mitochondrial basis of aging. Mol. Cell 61 (5), 654–666. https://doi.org/10.1016/j.molcel.2016.01.028.
Sunderland, P., Augustyniak, J., Lenart, J., et al., 2020. ATM-deficient neural precursors develop senescence phenotype with disturbances in autophagy. Mech. Ageing Dev. 190, 111296 https://doi.org/10.1016/j.mad.2020.111296.
Takubo, K., Ohmura, M., Azuma, M., et al., 2008. Stem cell defects in ATM-deficient undifferentiated spermatogonia through DNA damage-induced cell-cycle arrest. Research Support, Non-U.S. Gov't. Cell Stem Cell 2 (2), 170–182. https://doi.org/10.1016/j.stem.2007.10.023.
Tal, E., Alfo, M., Zha, S., et al., 2018. Inactive Atm abrogates DSB repair in mouse cerebellum more than does Atm loss, without causing a neurological phenotype. DNA Repair 72, 10–17. https://doi.org/10.1016/j.dnarep.2018.10.001.
Tang, S., Hou, Y., Zhang, H., et al., 2015. Oxidized ATM promotes abnormal proliferation of breast CAFs through maintaining intracellular redox homeostasis and activating the PI3K-AKT, MEK-ERK, and Wnt-beta-catenin signaling pathways. Cell Cycle 14 (12), 1908–1924. https://doi.org/10.1080/15384101.2015.1041685.
Taylor, A.M.R., Rothblum-Oviatt, C., Ellis, N.A., et al., 2019. Chromosome instability syndromes. Nat. Rev. Dis. Prim. 5 (1), 64. https://doi.org/10.1038/s41572-019-0113-0.
Taylor, A.M., Harnden, D.G., Arlett, C.F., et al., 1975. Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. Nature 258 (5534), 427–429.
Tong, A.S., Stern, J.L., Sfeir, A., et al., 2015. ATM and ATR Signaling Regulate the Recruitment of Human Telomerase to Telomeres. Cell Rep. 13 (8), 1633–1646. https://doi.org/10.1016/j.celrep.2015.10.041.

Tubbs, A., Nussenzweig, A., 2017. Endogenous DNA Damage as a Source of Genomic Instability in Cancer. Cell 168 (4), 644–656. https://doi.org/10.1016/j.cell.2017.01.002.

Tzur-Gilat, A., Ziv, Y., Mittelman, L., Barzilai, A., Shiloh, Y., 2013. Studying the cerebellar DNA damage response in the tissue culture dish (Oct). Mech. Ageing Dev. 134 (10), 496–505. https://doi.org/10.1016/j.mad.2013.04.001.

Valentin-Vega, Y.A., Maclean, K.H., Tait-Mulder, J., et al., 2012. Mitochondrial dysfunction in ataxia-telangiectasia. Feb 9 Blood 119 (6), 1490–1500. https://doi.org/10.1182/blood-2011-08-373639.

van Steensel, B., Belmont, A.S., 2017. Lamina-associated domains: links with chromosome architecture, heterochromatin, and gene repression. Cell 169 (5), 780–791. https://doi.org/10.1016/j.cell.2017.04.022.

Vijg, J., 2021. From DNA damage to mutations: all roads lead to aging. Ageing Res Rev. 68, 101316 https://doi.org/10.1016/j.arr.2021.101316.

Vizioli, M.G., Liu, T., Miller, K.N., et al., 2020. Mitochondria-to-nucleus retrograde signaling drives formation of cytoplasmic chromatin and inflammation in senescence. Genes Dev. 34 (5–6), 428–445. https://doi.org/10.1101/gad.331272.119.

Volkow, N.D., Tomasi, D., Wang, G.J., Studentsova, Y., Margus, B., Crawford, T.O., 2014. Brain glucose metabolism in adults with ataxia-telangiectasia and their asymptomatic relatives. Brain 137 (Pt 6), 1753–1761. https://doi.org/10.1093/brain/awu092.

Voss, S., Pietzner, J., Hoche, F., et al., 2014. Growth retardation and growth hormone deficiency in patients with Ataxia telangiectasia. Growth Factors 32 (3–4), 123–129. https://doi.org/10.3109/08977194.2014.939805.

Waterman, D.P., Haber, J.E., Smolka, M.B., 2020. Checkpoint responses to DNA double-strand breaks. Annu Rev. Biochem 89, 103–133. https://doi.org/10.1146/annurev-biochem-011520-104722.

Watson, J.D., 1972. Origin of concatemeric T7 DNA. Nat. N. Biol. 239 (94), 197–201.

White, M.C., Holman, D.M., Boehm, J.E., Peipins, L.A., Grossman, M., Henley, S.J., 2014. Age and cancer risk: a potentially modifiable relationship. Am. J. Prev. Med 46 (3 Suppl 1), S7–S15. https://doi.org/10.1016/j.amepre.2013.10.029.

Wong, K.K., Maser, R.S., Bachoo, R.M., et al., 2003. Telomere dysfunction and Atm deficiency compromises organ homeostasis and accelerates ageing. Nature 421 (6923), 643–648. https://doi.org/10.1038/nature01385.

Wood, L.D., Halvorsen, T.L., Dhar, S., et al., 2001. Characterization of ataxia telangiectasia fibroblasts with extended life-span through telomerase expression. Jan 18 Oncogene 20 (3), 278–288. https://doi.org/10.1038/sj.onc.1204072.

Wood, L.M., Sankar, S., Reed, R.E., et al., 2011. A novel role for ATM in regulating proteasome-mediated protein degradation through suppression of the ISG15 conjugation pathway. PLoS One 6 (1), e16422. https://doi.org/10.1371/journal.pone.0016422.

Xia, S.J., Shammas, M.A., Shmookler Reis, R.J., 1996. Reduced telomere length in ataxia-telangiectasia fibroblasts. Mutat. Res 364 (1), 1–11. https://doi.org/10.1016/0921-8777(96)00015-8.

Yan, P., Li, Z., Xiong, J., et al., 2021. LARP7 ameliorates cellular senescence and aging by allosterically enhancing SIRT1 deacetylase activity. Cell Rep. 37 (8), 110038 https://doi.org/10.1016/j.celrep.2021.110038.

Yang, B., Dan, X., Hou, Y., et al., 2021. NAD(+) supplementation prevents STING-induced senescence in ataxia telangiectasia by improving mitophagy. Aging Cell 20 (4), e13329. https://doi.org/10.1111/acel.13329.

Yang, H., Wang, H., Ren, J., Chen, Q., Chen, Z.J., 2017. cGAS is essential for cellular senescence. Proc. Natl. Acad. Sci. USA 114 (23), E4612–E4620. https://doi.org/10.1073/pnas.1705499114.

Yeo, A.J., Chong, K.L., Gatei, M., et al., 2021a. Impaired endoplasmic reticulum-mitochondrial signaling in ataxia-telangiectasia. iScience 24 (1), 101972. https://doi.org/10.1016/j.isci.2020.101972.

Yeo, A.J., Subramanian, G.N., Chong, K.L., et al., 2021b. An anaplerotic approach to correct the mitochondrial dysfunction in ataxia-telangiectasia (A-T). Mol. Metab. 54, 101354 https://doi.org/10.1016/j.molmet.2021.101354.

Yeung, F., Hoberg, J.E., Ramsey, C.S., et al., 2004. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 23 (12), 2369–2380. https://doi.org/10.1038/sj.emboj.7600244.

Zhang, W., Qu, J., Liu, G.H., Belmonte, J.C.I., 2020. The ageing epigenome and its rejuvenation. Nat. Rev. Mol. Cell Biol. 21 (3), 137–150. https://doi.org/10.1038/s41580-019-0204-5.

Zhang, Y., Lee, J.H., Paull, T.T., et al., 2018. Mitochondrial redox sensing by the kinase ATM maintains cellular antioxidant capacity. Sci. Signal 11 (538). https://doi.org/10.1126/scisignal.aaq0702.