Ageing Research Reviews 33 (2017) 76–88

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Ataxia-telangiectasia (A-T): An emerging dimension of premature ageing

Yosef Shiloh[a,*], Howard M. Lederman[b]

[a] The David and Inez Myers Laboratory for Cancer Research, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel
[b] Division of Pediatric Allergy and Immunology, The Johns Hopkins Medical Institutions, 600 N. Wolfe Street, Baltimore, MD 21287, USA

ARTICLE INFO

Article history:
Received 1 April 2016
Received in revised form 2 May 2016
Accepted 10 May 2016
Available online 12 May 2016

Keywords:
Ataxia-telangiectasia
ATM
DNA damage response
Protein kinase
Ageing

ABSTRACT

A-T is a prototype genome instability syndrome and a multifaceted disease. A-T leads to neurodegeneration – primarily cerebellar atrophy, immunodeficiency, oculocutaneous telangiectasia (dilated blood vessels), vestigial thymus and gonads, endocrine abnormalities, cancer predisposition and varying sensitivity to DNA damaging agents, particularly those that induce DNA double-strand breaks. With the recent increase in life expectancy of A-T patients, the premature ageing component of this disease is gaining greater awareness. The complex A-T phenotype reflects the ever growing number of functions assigned to the protein encoded by the responsible gene – the homeostatic protein kinase, ATM. The quest to thoroughly understand the complex A-T phenotype may reveal yet elusive ATM functions.

Contents

1. A-T and its genetic basis: a theme with many variations

1.1. The classical A-T phenotype

A-T (OMIM#208900) is an extensively documented genome instability syndrome found worldwide with incidence of 1:40,000–1:200,000 live births in different human populations. The clinical phenotype of A-T ranges from severe to milder variants of the disease, but is usually portrayed by its classical, severe form (Chun and Gatti, 2004; Crawford, 1998; Lavin, 2008; Nissenkorn and Ben-Zeev, 2015; Perlman et al., 2012). However, awareness is growing of the broad clinical variability associated with the causative mutations (Taylor et al., 2015). The primary cause of all variants of the disease is mutations in the autosomal gene *ATM* (A-T, mutated) at11q22-23 (Gatti et al., 1988; Savitsky et al., 1995a), which encodes the ATM protein (Savitsky et al., 1995b; Ziv et al., 1997) – a multi-functional protein kinase (Ditch and Paull, 2012; Guleria and Chandna, 2015; Shiloh, 2014; Shiloh and Ziv, 2013).

* Corresponding author.
E-mail address: yossih@post.tau.ac.il (Y. Shiloh).

http://dx.doi.org/10.1016/j.arr.2016.05.002
1568-1637/

The prominent symptom of classical A-T is progressive cerebellar ataxia that develops into a general motor dysfunction, eventually confining most patients to a wheelchair around the end of their first decade (Boder, 1985; Boder and Sedgwick, 1958; Chun and Gatti, 2004; Crawford, 1998; Crawford et al., 2000; Gatti, 1995; Nissenkorn and Ben-Zeev, 2015; Sedgwick and Boder, 1960; Verhagen et al., 2012b). Impairment of the extrapyramidal movement system is common in A-T, as are oculomotor abnormalities such as apraxia, strabismus and nystagmus. Swallowing and articulation of speech are often abnormal, and facial expression is limited. Dysfunctional swallowing is often associated with a general nutritional problem as well as clinically unapparent aspiration, which is thought to play a role in the increasing frequency of lower respiratory tract infections in many patients (Bhatt et al., 2015; Lefton-Greif et al., 2000). An absence of deep reflexes and peripheral neuropathy are common in A-T, but usually develop relatively later than other neurological impairments (Nissenkorn and Ben-Zeev, 2015). The main underlying pathology appears to be progressive cerebellar cortical degeneration that primarily affects Purkinje and granule neurons, but also basket cells (Gatti and Vinters, 1985; Vinters et al., 1985).

Oculocutaneous telangiectasia (dilated blood vessels) appear at various ages, usually in the eyes and sometimes on the ears and facial skin (Greenberger et al., 2013; Perlman et al., 2012). Immunodeficiency is another hallmark of A-T. Typically, IgA, IgE and various IgG subclasses are reduced; a diminished lymphocyte count is common, affecting B and T but not natural killer cells, and many have impaired antibody responses to vaccines (Gatti, 1995; Gatti et al., 1982; Hartlova et al., 2015; Nowak-Wegrzyn et al., 2004; Weaver and Gatti, 1985). The thymus is typically vestigial, as are the gonads. Another prominent clinical hallmark of A-T is cancer predisposition, with most malignancies being lymphoreticular of both B cell and T cell origin, including non-Hodgkin's lymphoma, Hodgkin's lymphoma, and several forms of leukemia (Loeb et al., 2000; Murphy et al., 1999; Olsen et al., 2001; Taylor and Edwards, 1982). A wide range of carcinomas has been reported in individual cases, especially among older patients. Many children with A-T grow at a diminished rate, and puberty is often delayed; this growth retardation was suggested to result from a primary endocrine defect (Ehlayel et al., 2014; Pommerening et al., 2015; Schubert et al., 2005; Voss et al., 2014), or a primary growth defect (Nissenkorn et al., 2016), but is probably also a function of swallowing problems making eating an inefficient and exhausting task. An important endocrine abnormality in some patients is insulin-resistant diabetes (Blevins and Gebhart, 1996; Morrell et al., 1986; Nissenkorn et al., 2016; Schalch et al., 1970). Notable laboratory findings are elevation of serum alpha fetoprotein and serum carcinoembryonic antigen. Further aspects of A-T, which entail segmental premature ageing, will be discussed later in this review, after the physiological functions of ATM are described.

A-T is a prototype genome instability syndrome (Butterworth and Taylor, 1986; Chun and Gatti, 2004; Crawford, 1998; Kennaugh et al., 1986; Lavin, 2008; Perlman et al., 2012; Taylor, 1978; Taylor and Edwards, 1982; Taylor et al., 2014). A-T patients show a striking sensitivity to the cytotoxic effect of ionizing radiation (Gotoff et al., 1967; Morgan et al., 1968). Cells from A-T patients exhibit marked chromosomal instability and sensitivity to ionizing radiations and radiomimetic chemicals (Chen et al., 1978; Shiloh et al., 1982a, 1983; Taylor, 1978; Taylor et al., 1975, 1979). This acute sensitivity results from a profound defect in the cellular response to DNA double-strand breaks (DSBs), whose chief mobilizer is the ATM protein (see below). It is important to note, however, that A-T cells are also moderately sensitive to a wide array of other DNA damaging agents suggesting that these cells cope less efficiently with many other DNA lesions besides DSBs (see below).

Lymphocyte cultures from A-T patients often contain clonal translocations that mainly involve the loci of the T-cell receptor and immunoglobulin heavy-chain genes (Butterworth and Taylor, 1986; Heppell et al., 1988; Kennaugh et al., 1986; Kojis et al., 1991; Taylor and Butterworth, 1986), pointing to a defect in the maturation of these genes via V(D)J and class-switch recombination in the adaptive immune system. Such clones usually herald the onset of malignancy and expand as malignancy progresses. Cultured A-T cell strains exhibit elevated rates of chromosome end associations and reduced telomere length (Metcalfe et al., 1996; Pandita et al., 1995; Smilenov et al., 1999; Vaziri, 1997; Wood et al., 2001). A-T fibroblast strains exhibit similar growth properties to wild-type cells at early passage levels but senesce prematurely(Shiloh et al., 1982b).

Increasing numbers of reports have described elevated readouts of oxidative stress in plasma of A-T patients (Reichenbach et al., 2002), in cultured A-T fibroblasts (Gatei et al., 2001; Lee et al., 2001) and lymphocytes (Ludwig et al., 2013), and in tissues and cultured cells from Atm-deficient mice (Barlow et al., 1999; Chen et al., 2003; Gage et al., 2001; Kamsler et al., 2001; Liu et al., 2005; McDonald et al., 2011; Reliene et al., 2004; Reliene and Schiestl, 2007; Ziv et al., 2005). Notably, the response of A-T fibroblast strains to induced oxidative stress was found defective (Ward et al., 1994; Yi et al., 1990). These observations were later linked to the role of ATM in regulating cellular oxidative stress (see below).

1.2. The ATM gene and ATM mutations underlying variations of the A-T phenotype

The *ATM* gene extends over 184 kb and contains 66 exons producing a 13 kb mRNA (Platzer et al., 1997; Uziel et al., 1996). It is extremely rich in sequence variations. Patients with the severe form of A-T are homozygous or compound heterozygous for null *ATM* alleles. The corresponding mutations usually lead to truncation of the ATM protein and subsequently to its loss due to instability of the truncated derivatives; a smaller portion of the mutations create amino acid substitutions that abolish ATM's catalytic activity (Barone et al., 2009; Gilad et al., 1996; Sandoval et al., 1999; Taylor et al., 2014) (see also http://chromium.liacs.nl/LOVD2/home.php?select_db=ATM).

Careful inspection of the neurological symptoms of A-T patients reveals variability in their age of onset and rate of progression among patients with different combinations of null *ATM* alleles (Alterman et al., 2007; Crawford et al., 2000; Taylor et al., 2015). Thus, despite the identical outcome in terms of ATM function, additional genes may affect the most cardinal symptom of A-T. Other, milder types of *ATM* mutations further extend this variability, and account for forms of the disease with extremely variable severity and age of onset of symptoms. The corresponding *ATM* genotypes are combinations of hypomorphic alleles or combinations of null and hypomorphic ones. Many of the latter are leaky splicing mutations and others are missense mutations, eventually yielding low amounts of active ATM (Alterman et al., 2007; Claes et al., 2013; Gilad et al., 1998; Meneret et al., 2014; Nakamura et al., 2014; Saunders-Pullman et al., 2012; Silvestri et al., 2010; Soresina et al., 2008; Taylor et al., 2014; Verhagen et al., 2009, 2012a; Worth et al., 2013). Notably, another distinct disorder, A-T-like disease (A-TLD) (Taylor et al., 2004), is clinically similar to mild A-T. A-TLD is caused by hypomorphic mutations in the *MRE11* gene (Stewart et al., 1999; Taylor et al., 2004), which encodes the MRE11 nuclease. MRE11 is part of the MRE11-RAD50-NBS1 (MRN) complex – a major DSB sensor (Rein and Stracker, 2014; Stracker and Petrini, 2011). The phenotypic similarity between mild A-T and A-TLD is due at least in part to the dependence of ATM activation by DSBs on MRN (Falck et al., 2005; Paull, 2015; Uziel et al., 2003).

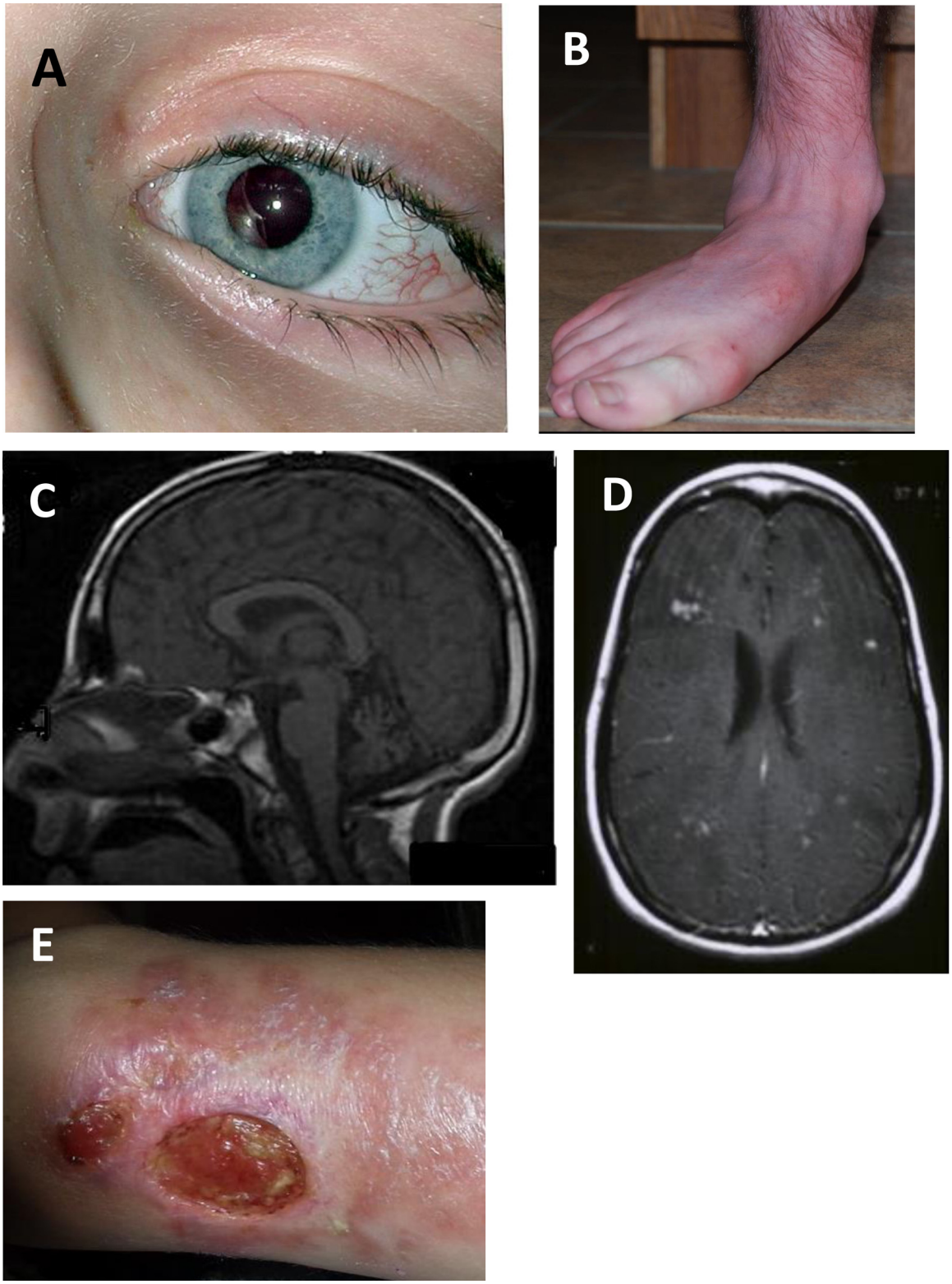

Fig. 1. Age-related abnormalities in A-T patients. A. Ocular telangiectasia. B. Foot deformity due to length-dependent neuropathy. C. Cerebellar atrophy. D. Intracerebral telangiectasia with multiple punctate hemosiderin deposits. E. Cutaneous granuloma.

2. The premature ageing facet of A-T

2.1. Segmental premature ageing in A-T patients

The name "ataxia-telangiectasia", was coined by Elena Boder and Robert Sedgwick in the first comprehensive description of the disease published in 1958 (Boder and Sedgwick, 1958). In an overview of A-T 27 years later (Boder, 1985), Dr. Boder wrote: "The clinical and pathological findings, including the gliovascular malformations in the CNS described recently in autopsies on older patients, reveal that A-T is characterized throughout its course by multisystemic progeric changes. It is proposed, therefore, that A-T

can serve as a model for the study of premature ageing." Importantly, the broad immune system defects in A-T have been regarded as a reflection of premature ageing of this system in these patients (Carney et al., 2012; Exley et al., 2011). Finding 'striking similarities between the immune system phenotypes of A-T patients and the elderly', (Carney et al., 2012) concluded that the immune system of A-T patients is congenitally aged, and (Exley et al., 2011) suggested that A-T could be viewed as a model of immune ageing. Similarly, the resemblance between ageing-associated decline of brain functionality and neurodegeneration associated with genome instability has recently been highlighted (Barzilai et al., 2016).

Adolescents and young adults with A-T exhibit an array of health problems that are typically not seen until late middle age or later. Among 53 A-T patients with mean age of 14.6 years (range 5.9–26.1), 43% had elevated serum transaminases, 39% of those patients had fatty liver detected by ultrasound, and 33% of the latter group developed steatohepatitis, fibrosis or cirrhosis (Weiss et al., 2015). There was also an increased incidence of dyslipidemia (10/52 = 19%) and diabetes (2/52 = 4%) (Nissenkorn et al., 2016). These abnormalities together with elevated levels of C-reactive protein suggest a diagnosis of metabolic syndrome in a substantial number of young A-T patients. The most common malignancies in A-T patients of all ages are of lymphocytic origin. However, among those from 18 to 40 years old with cancer, 11/21 (52%) had cancers of solid organs (stomach, esophagus, liver, parotid gland, thyroid, skin, breast and lung) that are rarely seen in that age group among people without A-T (HM Lederman, L Chessa, unpublished observations). There is a striking incidence of gammopathy in A-T (Sadighi Akha et al., 1999), another abnormality that is rarely seen in people <30 years old. Progeric features of skin include premature greying and thinning of hair, thinning of skin, and vitiligo (Reed et al., 1966). Osteoporosis is common because of a lack of weight bearing, nutritional deficiencies, and early gonadal failure in females. Incapacitating fatigue affects a majority of A-T patients over the age of 30. The etiology of this problem is likely to be multifactorial, with contributions from the extra effort required to function with neurodegeneration, and central nervous system effects of elevated levels of pro-inflammatory cytokines including IL-6 and IL-8 (McGrath-Morrow et al., 2016) and chronic, elevated levels of Type I interferons (Hartlova et al., 2015). Finally, telangiectasia appear in the brain and other internal organs of young adults with A-T, a peculiar finding seen in people without A-T only as a late effect of treatment with ionizing radiation for cancer therapy (Lin et al., 2014). Some of the ageing-related manifestations of A-T are shown in Fig. 1.

2.2. *The premature senescence component in the A-T cellular phenotype*

The cellular phenotype of A-T represents genome instability, deficient DNA damage response (DDR), and elevated oxidative stress, in addition to a premature senescence component, which was noticed early on (Shiloh et al., 1982b). Examination of a model of premature ageing inevitably includes the question, whether cellular senescence is involved. The hallmark of cellular senescence is an irreversible arrest of cellular proliferation. It can be induced by various stresses, has been implicated in development, wound healing, tissue repair and ageing (reviewed in (Campisi, 2013; Campisi and Robert, 2014; Demaria et al., 2014; Loaiza and Demaria, 2016; Munoz-Espin and Serrano, 2014; Salama et al., 2014; van Deursen, 2014; Velarde et al., 2013)). The main pathways that lead to this process are governed by two tumor suppressor axes: the p53-p21 axis and the $p16^{INK4a}$-pRB axis. Importantly, the senescent state was recently found to be very dynamic due to a senescence-associated secretory phenotype (SASP) – the secretion by senescent cells of an array of cytokines, growth factors and proteases that promote tissue repair and regeneration or inflammation (Campisi, 2011, 2013; Demaria et al., 2014; Loaiza and Demaria, 2016; Muñoz-Espín and Serrano, 2014; Rodier et al., 2009; Salama et al., 2014). Importantly, the SASP does not depend on p53 or $p16^{INK4a}$, and a major regulator of this process was recently found to be stabilization of the transcription factor GATA4, which starts a process that eventually enhances an NF-κB inflammatory process (Kang et al., 2015).

Evidence is mounting that senescent cells accumulate during ageing (Adams, 2009; Bernardes de Jesus and Blasco, 2012; Bhatia-Dey et al., 2016; Byun et al., 2015; Campisi, 2011; Loaiza and Demaria, 2016; Lopez-Otin et al., 2013; Muñoz-Espín and Serrano, 2014; Ovadya and Krizhanovsky, 2014; Sharpless and Sherr, 2015; van Deursen, 2014; Zhu et al., 2014). These senescent cells are associated with many age-related pathologies, including cancer (Campisi, 2013; Di Mitri and Alimonti, 2016; Lasry and Ben-Neriah, 2015; Ovadya and Krizhanovsky, 2014; van Deursen, 2014). The primary reason for this association is that the chronic presence of senescent cells and a persistent SASP cause local and systemic inflammation, which fuels a variety of age-related diseases. Evidence for this has been obtained in a number of mouse models (Baker et al., 2011; Bhatia-Dey et al., 2016; Byun et al., 2015; Campisi, 2013; Campisi and Robert, 2014; Kennedy et al., 2014; Lasry and Ben-Neriah, 2015; Loaiza and Demaria, 2016; Ovadya and Krizhanovsky, 2014; Zhu et al., 2014, 2015). Among the most potent inducers of the SASP are genotoxic stresses and conditions that lead to persistent DNA damage signaling (Kang et al., 2015; Rodier et al., 2009). Notably, ATM-deficient tissues and cultured cells exhibit signs of persistent stress reflected as ongoing, low-level DDR (Gatei et al., 2001), stress-associated gene expression patterns (Rashi-Elkeles et al., 2006; Weizman et al., 2003) and alteration in nicotine adenine dinucleotide balance (Stern et al., 2002). Thus, the senescence response, and particularly the SASP, is a strong candidate for linking ageing phenotypes and age-related rises in genotoxic stress (Lasry and Ben-Neriah, 2015; Maslov et al., 2013; Ovadya and Krizhanovsky, 2014; Vijg and Campisi, 2008).

The observation of accelerated telomere shortening and telomere fusions in peripheral blood lymphocytes (Metcalfe et al., 1996) and cultured fibroblasts (Smilenov et al., 1997; Xia et al., 1996) from A-T patients and cell lines expressing dominant-negative ATM fragments (Smilenov et al., 1997) exposed an important possible contributor to premature senescence of ATM-deficient cells. Ectopic expression of the catalytic subunit of telomerase (hTERT) rescued the telomere shortening and some premature senescence features of ATM-deficient cells without relieving the basic defect in the DSB response (Naka et al., 2004; Wood et al., 2001). Concomitant elimination of Atm and the telomerase RNA component (Terc) led to markedly accelerated premature ageing in mice compared to elimination of Terc alone (Wong et al., 2003). The wealth of information currently available on telomere maintenance and the role of the DDR in telomere dynamics (reviewed in (Arnoult and Karlseder, 2015; Doksani and de Lange, 2014; Webb et al., 2013)) has tightly linked ATM to telomere homeostasis and added an important component to the ageing aspect of A-T.

3. A-T carriers: enhanced morbidity?

Symptoms of autosomal, apparently recessive disorders often appear in subtle forms in carriers of the corresponding mutations. Carriers of A-T mutations have long been a focus of interest for epidemiologic geneticists. Their frequency in the US population has been estimated at 2–3% (Swift et al., 1986) but may be closer to 1%. Importantly, cells from A-T carriers show variable degrees of sensitivity to IR and radiomimetic chemicals, and chromosomal instability, intermediate between those of cells from unrelated con-

trols and cells from A-T patients (Chen et al., 1978; Cohen et al., 1975; Cole et al., 1988; Fernet et al., 2004; Neubauer et al., 2002; Parshad et al., 1985; Pernin et al., 1999; Rosin et al., 1989; Sanford et al., 1990; Scott et al., 1996; Shigeta et al., 1999; Shiloh et al., 1989, 1986, 1982a,c; Speit et al., 2000; Takai et al., 1990). This sensitivity may be expressed in the carriers as an adverse effect of radiation therapy (Varghese et al., 1999). Chromosomal breakage was noticed in epithelial tissues and peripheral blood lymphocytes of A-T carriers (Rosin and Ochs, 1986, 1989; Shiloh et al., 1986). Fibroblasts from A-T carriers show enhanced cellular senescence, which again is intermediate between that of control individuals and A-T patients (Shiloh et al., 1982b). Notably, mice heterozygous for *Atm* null mutations are more sensitive to radiation-induced cytotoxicity, cataracts and oncogenesis than animals homozygous for the wild-type *Atm* (Smilenov et al., 2001; Worgul et al., 2002, 2005).

For the past four decades the possible predisposition of A-T carriers to breast and other cancers has been extensively studied and debated, with variable and often conflicting results (d'Almeida et al., 2005; Goldgar et al., 2011; Paglia et al., 2010; Swift et al., 1990; Swift and Lukin, 2008; Thompson et al., 2005; van Os et al., 2016) and references therein. Importantly, within this wealth of publications on possible cancer predisposition of A-T carriers, two reports described increased deaths from ischemic heart disease among these individuals (Su and Swift, 2000; Swift and Chase, 1983). A recent *meta*-analysis of these studies (van Os et al., 2016) concluded A-T carriers have a reduced life expectancy because of mortality from cancer and ischemic heart diseases (RR 1.7, 95% CI 1.2–2.4) and an increased risk of developing cancer (RR 1.5, 95% CI 0.9–2.4), in particular breast cancer (RR women 3.0, 95% CI 2.1–4.5). These observations raise the question whether A-T carriers do indeed harbor the premature ageing aspect of A-T and call for large-scale epidemiologic studies of A-T carriers focused on ageing-associated morbidity. Notably, two reports recently linked a specific single nucleotide polymorphism (SNP) in the *ATM* gene promoter to increased longevity in Chinese and Italian populations (Chen et al., 2010; Piaceri et al., 2013).

4. Do the known ATM functions account for the A-T phenotype?

As in many genetic disorders, the responsible gene and its protein product were identified as a result of the attempt to understand the disease (Savitsky et al., 1995a). Does the information on ATM functions that has accumulated since then explain the A-T phenotype in full?

ATM is a homeostatic protein kinase with an extremely broad range of roles in various cellular circuits (Ambrose and Gatti, 2013; Awasthi et al., 2015; Cremona and Behrens, 2014; Espach et al., 2015; Guleria and Chandna, 2015; Shiloh, 2014; Shiloh and Ziv, 2013) (Fig. 2). This large polypeptide of 350 kDa and 3056 residues bears a PI3 kinase signature within its carboxy-terminal catalytic site, but has the catalytic activity of a serine-threonine protein kinase. This motif is characteristic of a protein family of which ATM is a member – the PI-3 kinase-like protein kinases (PIKKs) (Baretic and Williams, 2014; Lovejoy and Cortez, 2009). This family also contains the mTOR protein, which regulates many signaling pathways in response to nutrient levels, growth factors and energy balance (Alayev and Holz, 2013; Cornu et al., 2013); the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs), which is involved in the NHEJ pathway of DSB repair and other genotoxic stress responses (Davis et al., 2014; Jette and Lees-Miller, 2015), SMG-1, which plays a key role in nonsense-mediated mRNA decay (Yamashita et al., 2005); and ATR, which responds to stalled replication forks and a variety of DNA lesions that lead to the formation of single-stranded DNA, including deeply resected DSBs (Awasthi et al., 2016; Errico and Costanzo, 2012; Marechal and Zou, 2013). The redundancy, crosstalk and collaboration between the latter three PIKKs, which collectively respond to a broad spectrum of genotoxic stresses, are being extensively investigated (Chen et al., 2012; Gobbini et al., 2013; Lovejoy and Cortez, 2009; Marechal and Zou, 2013; Sirbu and Cortez, 2013; Thompson, 2012).

It should be noted that in A-T patients, the two PIKKs that converse and cooperate with ATM in the response to genotoxic stress, ATR and DNA-PK, remain active. In view of the functional relationships between the three protein kinases, some of ATM's duties are probably carried out to a certain extent by ATR and/or DNA-PK, in A-T cells. On the other hand, the lack of a very versatile member of this trio may lead to some suboptimal responses of the other two, if they depend on the crosstalk with ATM. This interesting question is a subject of intensive research.

The most widely documented function of ATM, and the one associated with its most vigorous activation, is the mobilization of the complex signaling network that responds to DSBs in the DNA (Awasthi et al., 2015; Cremona and Behrens, 2014; McKinnon, 2012; Shiloh and Ziv, 2013; Thompson, 2012). DSBs are induced by exogenous DNA breaking agents or endogenous reactive oxygen species (Schieber and Chandel, 2014), and are an integral part of physiological processes including meiotic recombination (Borde and de Massy, 2013; Lange et al., 2011) and the rearrangement of antigen receptor genes in the adaptive immune system (Alt et al., 2013). DSBs are repaired via nonhomologous end-joining (NHEJ), or homologous recombination repair (HRR) (Chapman et al., 2012; Jasin and Rothstein, 2013; Radhakrishnan et al., 2014; Shibata and Jeggo, 2014). DSBs also activates the DDR, a vast signaling network that mobilizes special cell cycle checkpoints, extensively alters the cellular transcriptome, and changes the turnover, activity and function of numerous proteins that ultimately leads to modulation of numerous cellular circuits. This network is based on a core of dedicated DDR players and the *ad-hoc* recruitment of proteins from many other arenas of cellular metabolism, which typically undergo special, damage-induced post-translational modifications (PTMs) (Goodarzi and Jeggo, 2013; Panier and Durocher, 2013; Polo and Jackson, 2011; Shiloh and Ziv, 2013; Sirbu and Cortez, 2013; Thompson, 2012). Once ATM mobilizes the vast DDR network in response to a DSB (Bhatti et al., 2011; McKinnon, 2012; Shiloh and Ziv, 2013), its protein kinase activity is rapidly enhanced, and PTMs on the ATM molecule are induced, including several autophosphorylations and an acetylation (Bakkenist and Kastan, 2003; Bensimon et al., 2010; Bhatti et al., 2011; Kaidi and Jackson, 2013; Kozlov et al., 2006; Paull, 2015; Shiloh and Ziv, 2013; Sun et al., 2007). ATM subsequently phosphorylates key players in various arms of the DSB response network (Bensimon et al., 2011, 2010; Matsuoka et al., 2007; Mu et al., 2007; Shiloh and Ziv, 2013), including other protein kinases that in turn phosphorylate still other targets (Bensimon et al., 2011).

A broader, overarching role for ATM in maintaining genome stability was recently suggested by one of us (YS) in addition to mobilizing the DSB response (Shiloh, 2014). According to this conjecture, ATM supports other DNA repair pathways that respond to various genotoxic stresses, among them single-strand break repair (SSBR) (Khoronenkova and Dianov, 2015) and base excision repair (BER) – a cardinal pathway in dealing with the daily nuclear and mitochondrial DNA damage caused by endogenous agents (Bauer et al., 2015; Wallace, 2014). ATM's involvement in these processes is based on its ability to phosphorylate proteins that function in these pathways. In this way ATM also takes part also in resolving non-canonical DNA structures that arise in DNA metabolism, and in regulating other aspects of genome integrity such as nucleotide metabolism, the response to replication stress, and resolution of the occasional conflicts that arise between DNA damage and the transcription machinery. ATM is not critical for any of these processes

in the same way it is for the DSB response, but rather contributes to their regulation (in most cases, their enhancement) when the need arises (Segal-Raz et al., 2011; Shiloh, 2014; Zolner et al., 2011).

This function of ATM may explain the moderate, variable sensitivity of ATM-deficient cells to a broad range of DNA damaging agents. Among them are UV radiation, alkylating agents, crosslinking agents, hydrogen peroxide, 4-Nitroquinoline 1-oxide, phorbol-12-myristate-13-acetate and topoisomerase 1 poisons (Alagoz et al., 2013; Barfknecht and Little, 1982; Fedier et al., 2003; Hannan et al., 2002; Henderson and Ribecky, 1980; Hoar and Sargent, 1976; Jaspers et al., 1982; Katyal et al., 2014; Lee et al., 2006; Leonard et al., 2004; Mirzayans et al., 1989; Paterson et al., 1976; Scudiero, 1980; Shiloh et al., 1985; Smith et al., 1989; Smith and Paterson, 1980; Speit et al., 2000; Teo and Arlett, 1982; Ward et al., 1994; Yi et al., 1990; Zhang et al., 1996). ATM-deficient cells also exhibit reduced efficiency in resolving Topoisomerase I-DNA covalent intermediates (Alagoz et al., 2013; Katyal et al., 2014).

This ongoing role of ATM is its routine function in the daily maintenance of genome stability, while its powerful role in the DSB response is reserved for when this harmful lesion interferes with the daily life of a cell. Thus, when ATM is missing, not only is there markedly reduced response to DSBs, the ongoing modulation of numerous pathways in response to occasional stresses becomes suboptimal. All of these lesions are part of the daily wear and tear on the genome that contributes to ageing.

An additional role for ATM in genome dynamics was proposed following evidence that ATM is involved in shaping the epigenome in neurons by regulating the localization of the histone deacetylase 4 (HDAC4) (Herrup, 2013; Herrup et al., 2013; Li et al., 2012), targeting the EZH2 component of the polycomb repressive complex 2 (Li et al., 2013), and regulating the levels of 5-hydroxymethylcytosine in Purkinje cells (Jiang et al., 2015).

ATM's role in cellular homeostasis is further expanded by its cytoplasmic fraction. Specifically, cytoplasmic ATM was found to be associated with peroxisomes (Tripathi and Walker, 2016; Watters et al., 1999; Zhang et al., 2015) and mitochondria (Valentin-Vega et al., 2012). In view of the evidence of increased oxidative stress in ATM-deficient cells, it has long been suspected that ATM senses and responds to oxidative stress (Alexander et al., 2010a; Barzilai et al., 2002; Gatei et al., 2001; Rotman and Shiloh, 1997a,b; Takao et al., 2000; Watters, 2003). This conjecture was validated by work from the Paull lab (Guo et al., 2010b), which identified an MRN-independent mode of ATM activation, differentiating it from DSB-induced activation, stimulated by reactive oxygen species (ROS) and leading to ATM oxidation (Guo et al., 2010a,b; Lee et al., 2014; Paull, 2015). ATM was also found to be involved specifically in the protection against oxidative stress induced by oxidized low-density lipoprotein (Semlitsch et al., 2011). It has thus assumed the role of a redox sensor (Ditch and Paull, 2012; Kruger and Ralser, 2011; Tripathi and Walker, 2016). Recently, the first phospho-proteomic screen was carried out to identify substrates of ROS-activated ATM (Kozlov et al., 2015).

An important arm of the ATM-mediated response to ROS extends to peroxisomes (Tripathi and Walker, 2016). Work from the Walker lab showed that ROS-mediated activation of peroxisomal ATM leads to ATM-mediated phosphorylation of LKB and subsequent activation of AMPK and TSC2, which dampens mTORC1-mediated signaling, eventually decreasing protein synthesis and enhancing autophagy (Alexander et al., 2010a,b; Alexander and Walker, 2010; Tripathi et al., 2013; Zhang et al., 2013). Further work from this lab (Zhang et al., 2015) showed that ATM also phosphorylates the peroxisomal protein PEX5, flagging it for ubiquitylation and subsequent binding to the autophagy adapter, p62, in the process of autophagy-associated peroxisome degradation (pexophagy) – a critical process in peroxisome homeostasis (Till et al., 2012).

Still another arm of the ATM-mediated response to oxidative stress operates in the mitochondrial fraction of ATM. ATM is thus emerging also as a regulator of mitochondrial homeostasis. Evidence is accumulating of its involvement in mitochondrial function, mitophagy, and the integrity of mitochondrial DNA (Ambrose et al., 2007; D'Souza et al., 2013; Eaton et al., 2007; Fu et al., 2008; Sharma et al., 2014; Valentin-Vega and Kastan, 2012; Valentin-Vega et al., 2012) and further work is needed to identify its substrates in mitochondria and the mechanistic aspects of its action in this arena. Several laboratories recently described direct links between ATM and the SASP – a cardinal feature of cell senescence. Work from the Gamble lab (Chen et al., 2015) showed that the histone variant macroH2A.1 is required for full transcriptional activation of SASP-promoting genes, driving a positive feedback loop that enhances cell senescence. This response is countered by a negative feedback loop that involves ATM activation by endoplasmic reticulum stress, elevated ROS levels or DNA damage. ATM's activity is required for the removal of macroH2A.1 from sites of SASP genes, thus leading to SASP gene repression. The Elledge lab identified a major SASP activator – the transcription factor GATA4, whose stabilization drives this process (Kang et al., 2015). Importantly, the activation of this pathway was dependent on both ATM and ATR, as was senescence-associated activation of p53 and $p16^{INK4a}$. On the other hand, the Zhang lab (Aird et al., 2015) recently showed that when cell senescence is induced by replication stress (e.g., following nucleotide deficiency), ATM inactivation allows the cell to bypass senescence by shifting cellular metabolism: upon ATM loss, dNTP levels rise due to up-regulation of the pentose phosphate pathway, whose key regulator, glucose-6-phosphate dehydrogenase (G6PD) is under functional regulation by ATM (Aird et al., 2015; Cosentino et al., 2011).

Other metabolic arenas in which ATM involvement is gaining attention are insulin response and lipoprotein metabolism, clinically represented by the metabolic syndrome. This role of ATM in cellular physiology was recently thoroughly and convincingly reviewed (Espach et al., 2015). Briefly, ATM was found to participate in several signaling pathways mediated by insulin (Halaby et al., 2008; Jeong et al., 2010; Miles et al., 2007; Viniegra et al., 2005; Yang and Kastan, 2000); and heterozygosity for *Atm* null allele in ApoE-deficient mice was found to aggravate their metabolic syndrome (Mercer et al., 2010; Schneider et al., 2006; Wu et al., 2005) – an effect that was partly relieved by the mitochondria-targeted antioxidant MitQ (Mercer et al., 2012).

Another pathway by which ATM may impact on cellular senescence is the dependence of IGF-1 receptor expression on ATM (Ching et al., 2013; Goetz et al., 2011; Peretz et al., 2001); the mechanism remains to be elucidated, but ATM impacts on IGF-1-mediated pathways, including those that affect cellular senescence (Luo et al., 2014). Another series of observations assigned ATM a protective role in cardiac myocyte apoptosis stimulated by β-adrenergic receptor and myocardial remodeling. Loss of Atm in mice induced myocardial fibrosis and myocyte hypertrophy and interfered with cardiac remodeling following myocardial infarction (Daniel et al., 2014; Foster et al., 2013, 2011, 2012). The mechanistic aspects of these effects are still unclear, but ATM's apparent involvement in myocardial homeostasis might be relevant to the observation of elevated arteriosclerosis in A-T carriers (Su and Swift, 2000; Swift and Chase, 1983).

The cardinal function of ATM in the DSB response explains the radiation sensitivity and genome instability. The immunodeficiency, the nature of the clonal translocations in the lymphoid system and the predisposition to lymphoid malignancies are explained by the involvement of ATM in the response to the physiologic DSBs formed in the maturation of the adaptive immune system genes during lymphocyte development (reviewed in (Alt et al., 2013; Bednarski and Sleckman, 2012; Boboila et al., 2012)).

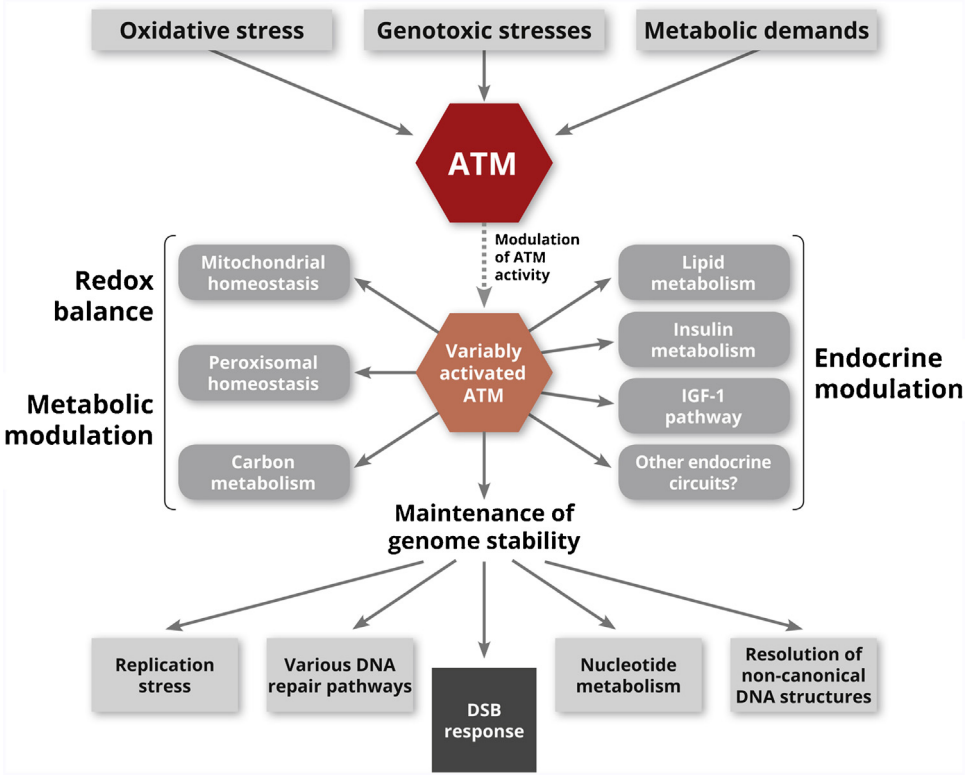

Fig. 2. Current view of ATM functions as a homeostatic protein kinase.

Likewise, the gonadal dysgenesis reflects the role of the DSB response in the processing of physiologic DSBs formed during the first meiosis (reviewed in (Borde and de Massy, 2013; Kim et al., 2016)). Explanation of the cerebellar atrophy – the cardinal clinical symptom of A-T – is still a subject of intense discussion. Is the ATM function whose loss contributes to this process associated with maintenance of genome stability, or with epigenome dynamics, or is it not associated at all with genome stability and is not nuclear (Guleria and Chandna, 2015; Herrup, 2013; Hoche et al., 2012; Shiloh, 2014; Shiloh and Ziv, 2013)? We attribute special importance in the cerebellar demise in A-T to ATM's comprehensive role in maintaining genome homeostasis (Shiloh, 2014), but will not elaborate on this here since this review is focused primarily on the ageing aspects of A-T.

From the foregoing summary of ATM functions it is clear that most of them impinge on physiological processes that have been tied to ageing (Ahlqvist et al., 2015; Bolt and Bergman, 2015; Feltes et al., 2015; Goldsmith, 2012; Jenny, 2012; Jones, 2015; Pinto and Moraes, 2015; Sergiev et al., 2015; Xi et al., 2013): the link between genome instability and ageing is solid (Behrens et al., 2014; Castells-Roca et al., 2015; Edifizi and Schumacher, 2015; Franzke et al., 2015; Gorbunova and Seluanov, 2016; Klement and Goodarzi, 2014; Maynard et al., 2015; Ribezzo et al., 2016; Vermeij et al., 2016; Vijg and Suh, 2013) and well reflected in the segmental, accelerated ageing observed in many genome instability syndromes and in mouse models of DNA repair deficiencies (Cleaver et al., 2009; Edifizi and Schumacher, 2015; Gregg et al., 2011; Gurkar and Niedernhofer, 2015; Maynard et al., 2015; Vermeij et al., 2014, 2016). The combination of defective maintenance of genome stability and impairment of other physiological functions caused by ATM loss (Fig. 2) is expected to yield a premature ageing phenotype: defective DDR, abnormal telomere dynamics, suboptimal regulation of redox balance and subsequent oxidative stress, defective peroxisomal and mitochondrial homeostasis, and defects in pathways that have been linked directly to ageing such as the IGF-1-mediated circuits (Kenyon, 2011). Notably, other endocrine abnormalities observed in A-T patients (Ehlayel et al., 2014; Pommerening et al., 2015; Schubert et al., 2005; Voss et al., 2014) may also enhance the detrimental effect of the above combination (Edifizi and Schumacher, 2015; Schiewer and Knudsen, 2016; Vermeij et al., 2016).

5. Future perspectives

The cross-talk between A-T patients' bedside and the laboratory bench has been extremely instrumental for understanding both the A-T phenotype and the physiological functions of ATM. In the early years of life, the A-T phenotype is dominated by devastating neurodegeneration, immunodeficiency and cancer predisposition, while the features of ageing are seen only later. Now that advances in care have increased the survival of many A-T patients into the third decade of life and beyond, this emerging aspect of the disease is demanding our attention. Further work on ATM biochemistry and the ever expanding network of ATM substrates, within and outside of the genome stability circle, is expected to identify ATM-dependent processes that affect ageing. Investigation of the ageing hallmarks that appear in adolescent A-T patients and the subtle premature ageing of A-T carriers is very timely now. The premature senescence of primary A-T fibroblasts requires deeper characterization using high-throughput 'omics' technologies. Mouse models combining *Atm* mutations with mutations in other genes that modulate ageing via various physiological circuits should also be instrumental in this regard. All in all, it is time to reconsider Dr. Boder's statement from 1985 (Boder, 1985): "A-T can serve as a model for the study of premature ageing".

Acknowledgments

We thank the following colleagues for critical reading of the manuscript: Yael Ziv, Andreea Nissenkorn, Martin Lavin, Valery Krizhanovsky, Luciana Chessa, Vilhelm Bohr, Ron Prywes, Ari Barzilai, Marina Alfo, Ron Jachimowicz, Efrat Tal, and Julia Shaknof. Work in the YS laboratory is funded by research grants from the A-T Children's Project, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, The A-T Ease Foundation, the Israel Science Foundation, The Israel Cancer Research Fund, and the I-CORE Program of the Planning and Budgeting Committee of the Israel Ministry of Education. YS is a Research Professor of the Israel Cancer Research Fund.

References

Adams, P.D., 2009. Healing and hurting: molecular mechanisms, functions and pathologies of cellular senescence. Mol. Cell 36, 2–14.
Ahlqvist, K.J., Suomalainen, A., Hamalainen, R.H., 2015. Stem cells, mitochondria and aging. Biochim. Biophys. Acta 1847, 1380–1386.
Aird, K.M., Worth, A.J., Snyder, N.W., Lee, J.V., Sivanand, S., Liu, Q., Blair, I.A., Wellen, K.E., Zhang, R., 2015. ATM couples replication stress and metabolic reprogramming during cellular senescence. Cell Rep. 11, 893–901.
Alagoz, M., Chiang, S.C., Sharma, A., El-Khamisy, S.F., 2013. ATM deficiency results in accumulation of DNA-topoisomerase I covalent intermediates in neural cells. PLoS One 8, e58239.
Alayev, A., Holz, M.K., 2013. mTOR signaling for biological control and cancer. J. Cell. Physiol. 228, 1658–1664.
Alexander, A., Walker, C.L., 2010. Differential localization of ATM is correlated with activation of distinct downstream signaling pathways. Cell Cycle 9, 3685–3686.
Alexander, A., Cai, S.L., Kim, J., Nanez, A., Sahin, M., MacLean, K.H., Inoki, K., Guan, K.L., Shen, J., Person, M.D., Kusewitt, D., Mills, G.B., Kastan, M.B., Walker, C.L., 2010a. ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. Proc. Natl. Acad. Sci. U.S.A. 107, 4153–4158.
Alexander, A., Kim, J., Walker, C.L., 2010b. ATM engages the TSC2/mTORC1 signaling node to regulate autophagy. Autophagy 6, 672–673.
Alt, F.W., Zhang, Y., Meng, F.L., Guo, C., Schwer, B., 2013. Mechanisms of programmed DNA lesions and genomic instability in the immune system. Cell 152, 417–429.
Alterman, N., Fattal-Valevski, A., Moyal, L., Crawford, T.O., Lederman, H.M., Ziv, Y., Shiloh, Y., 2007. Ataxia-telangiectasia: mild neurological presentation despite null ATM mutation and severe cellular phenotype. Am. J. Med. Genet. Part A 143A, 1827–1834.
Ambrose, M., Gatti, R.A., 2013. Pathogenesis of ataxia-telangiectasia: the next generation of ATM functions. Blood 121, 4036–4045.
Ambrose, M., Goldstine, J.V., Gatti, R.A., 2007. Intrinsic mitochondrial dysfunction in ATM-deficient lymphoblastoid cells. Hum. Mol. Genet. 16, 2154–2164.
Arnoult, N., Karlseder, J., 2015. Complex interactions between the DNA-damage response and mammalian telomeres. Nat. Struc. Mol. Biol. 22, 859–866.
Awasthi, P., Foiani, M., Kumar, A., 2015. ATM and ATR signaling at a glance. J. Cell Sci. 128, 4255–4262.
Awasthi, P., Foiani, M., Kumar, A., 2016. ATM and ATR signaling at a glance. J. Cell Sci. 129, 1285.
Baker, D.J., Wijshake, T., Tchkonia, T., LeBrasseur, N.K., Childs, B.G., van de Sluis, B., Kirkland, J.L., van deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236.
Bakkenist, C.J., Kastan, M.B., 2003. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature 421, 499–506.
Baretic, D., Williams, R.L., 2014. PIKKs–the solenoid nest where partners and kinases meet. Curr. Opin. Struct. Biol. 29, 134–142.
Barfknecht, T.R., Little, J.B., 1982. Hypersensitivity of ataxia telangiectasia skin fibroblasts to DNA alkylating agents. Mutat. Res. 94, 369–382.
Barlow, C., Dennery, P.A., Shigenaga, M.K., Smith, M.A., Morrow, J.D., Roberts, L.J., 2nd Wynshaw-Boris, A., Levine, R.L., 1999. Loss of the ataxia-telangiectasia gene product causes oxidative damage in target organs. Proc. Natl. Acad. Sci. U. S. A. 96, 9915–9919.
Barone, G., Groom, A., Reiman, A., Srinivasan, V., Byrd, P.J., Taylor, A.M., 2009. Modeling ATM mutant proteins from missense changes confirms retained kinase activity. Hum. Mutat. 30, 1222–1230.
Barzilai, A., Rotman, G., Shiloh, Y., 2002. ATM deficiency and oxidative stress: a new dimension of defective response to DNA damage. DNA Repair 1, 3–25.
Barzilai, A., Schumacher, B., Shiloh, Y., 2016. Genome instability: linking ageing and brain degeneration. Mech. Ageing Dev. (in press).
Bauer, N.C., Corbett, A.H., Doetsch, P.W., 2015. The current state of eukaryotic DNA base damage and repair. Nucleic Acids Res. 43, 10083–10101.
Bednarski, J.J., Sleckman, B.P., 2012. Lymphocyte development: integration of DNA damage response signaling. Adv. Immunol. 116, 175–204.
Behrens, A., van Deursen, J.M., Rudolph, K.L., Schumacher, B., 2014. Impact of genomic damage and ageing on stem cell function. Nat. Cell Biol. 16, 201–207.
Bensimon, A., Schmidt, A., Ziv, Y., Elkon, R., Wang, S.Y., Chen, D.J., Aebersold, R., Shiloh, Y., 2010. ATM-dependent and – independent dynamics of the nuclear phosphoproteome after DNA damage. Sci. Signal. 3, rs3.
Bensimon, A., Aebersold, R., Shiloh, Y., 2011. Beyond ATM: the protein kinase landscape of the DNA damage response. FEBS Lett. 585, 1625–1639.
Bernardes de Jesus, B., Blasco, M.A., 2012. Assessing cell and organ senescence biomarkers. Circ. Res. 111, 97–109.
Bhatia-Dey, N., Kanherkar, R.R., Stair, S.E., Makarev, E.O., Csoka, A.B., 2016. Cellular senescence as the causal nexus of aging. Front. Genet. 7, 13.
Bhatt, J.M., Bush, A., van Gerven, M., Nissenkorn, A., Renke, M., Yarlett, L., Taylor, M., Tonia, T., Warris, A., Zielen, S., Zinna, S., Merkus, P.J., 2015. ERS statement on the multidisciplinary respiratory management of ataxia telangiectasia. Eur. Respir. Rev. 24, 565–581.
Bhatti, S., Kozlov, S., Farooqi, A.A., Naqi, A., Lavin, M., Khanna, K.K., 2011. ATM protein kinase: the linchpin of cellular defenses to stress. Cell. Mol. Life Sci. CMLS 68, 2977–3006.
Blevins Jr., L.S., Gebhart, S.S., 1996. Insulin-resistant diabetes mellitus in a black woman with ataxia-telangiectasia. South. Med. J. 89, 619–621.
Boboila, C., Alt, F.W., Schwer, B., 2012. Classical and alternative end-joining pathways for repair of lymphocyte-specific and general DNA double-strand breaks. Adv. Immunol. 116, 1–49.
Boder, E., Sedgwick, R.P., 1958. Ataxia-telangiectasia; a familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. Pediatrics 21, 526–554.
Boder, E., 1985. Ataxia-telangiectasia: an overview. Kroc Found. Ser. 19, 1–63.
Bolt, K., Bergman, A., 2015. Systems biology of aging. Adv. Exp. Med. Biol. 847, 163–178.
Borde, V., de Massy, B., 2013. Programmed induction of DNA double strand breaks during meiosis: setting up communication between DNA and the chromosome structure. Curr. Opin. Genet. Dev. 23, 147–155.
Butterworth, S.V., Taylor, A.M., 1986. A subpopulation of t(2;14)(p11;q32) cells in ataxia telangiectasia B lymphocytes. Hum. Genet. 73, 346–349.
Byun, H.O., Lee, Y.K., Kim, J.M., Yoon, G., 2015. From cell senescence to age-related diseases: differential mechanisms of action of senescence-associated secretory phenotypes. BMB Rep. 48, 549–558.
Campisi, J., Robert, L., 2014. Cell senescence: role in aging and age-related diseases. Interdiscip. Top. Gerontol. 39, 45–61.
Campisi, J., 2011. Cellular senescence: putting the paradoxes in perspective. Curr. Opin. Genet. Dev. 21, 107–112.
Campisi, J., 2013. Aging, cellular senescence, and cancer. Annu. Rev. Physiol. 75, 685–705.
Carney, E.F., Srinivasan, V., Moss, P.A., Taylor, A.M., 2012. Classical ataxia telangiectasia patients have a congenitally aged immune system with high expression of CD95. J. Immunol. 189, 261–268.
Castells-Roca, L., Mueller, M.M., Schumacher, B., 2015. Longevity through DNA damage tolerance. Cell Cycle 14, 467–468.
Chapman, J.R., Taylor, M.R., Boulton, S.J., 2012. Playing the end game: DNA double-strand break repair pathway choice. Mol. Cell 47, 497–510.
Chen, P.C., Lavin, M.F., Kidson, C., Moss, D., 1978. Identification of ataxia telangiectasia heterozygotes, a cancer prone population. Nature 274, 484–486.
Chen, P., Peng, C., Luff, J., Spring, K., Watters, D., Bottle, S., Furuya, S., Lavin, M.F., 2003. Oxidative stress is responsible for deficient survival and dendritogenesis in purkinje neurons from ataxia-telangiectasia mutated mutant mice. J. Neurosci. 23, 11453–11460.
Chen, T., Dong, B., Lu, Z., Tian, B., Zhang, J., Zhou, J., Wu, H., Zhang, Y., Wu, J., Lin, P., Zhang, J., Xu, H., Mo, X., 2010. A functional single nucleotide polymorphism in promoter of ATM is associated with longevity. Mech. Ageing Dev. 131, 636–640.
Chen, B.P., Li, M., Asaithamby, A., 2012. New insights into the roles of ATM and DNA-PKcs in the cellular response to oxidative stress. Cancer Lett. 327, 103–110.
Chen, H., Ruiz, P.D., McKimpson, W.M., Novikov, L., Kitsis, R.N., Gamble, M.J., 2015. MacroH2A1 and ATM play opposing roles in paracrine senescence and the senescence-associated secretory phenotype. Mol. Cell 59, 719–731.
Ching, J.K., Luebbert, S.H., Collins, R.L.t., Zhang, Z., Marupudi, N., Banerjee, S., Hurd, R.D., Ralston, L., Fisher, J.S., 2013. Ataxia telangiectasia mutated impacts insulin-like growth factor 1 signalling in skeletal muscle. Exp. Physiol. 98, 526–535.
Chun, H.H., Gatti, R.A., 2004. Ataxia-telangiectasia, an evolving phenotype. DNA Repair 3, 1187–1196.
Claes, K., Depuydt, J., Taylor, A.M., Last, J.I., Baert, A., Schietecatte, P., Vandersickel, V., Poppe, B., De Leeneer, K., D'Hooghe, M., Vral, A., 2013. Variant ataxia telangiectasia: clinical and molecular findings and evaluation of radiosensitive phenotypes in a patient and relatives. Neuromol. Med. 15, 447–457.
Cleaver, J.E., Lam, E.T., Revet, I., 2009. Disorders of nucleotide excision repair: the genetic and molecular basis of heterogeneity. Nat. Rev. Genet. 10, 756–768.
Cohen, M.M., Shaham, M., Dagan, J., Shmueli, E., Kohn, G., 1975. Cytogenetic investigations in families with ataxia-telangiectasia. Cytogenet. Cell Genet. 15, 338–356.
Cole, J., Arlett, C.F., Green, M.H., Harcourt, S.A., Priestley, A., Henderson, L., Cole, H., James, S.E., Richmond, F., 1988. Comparative human cellular radiosensitivity: II. The survival following gamma-irradiation of unstimulated (G0) T-lymphocytes, T-lymphocyte lines, lymphoblastoid cell lines and fibroblasts from normal donors, from ataxia-telangiectasia patients and from ataxia-telangiectasia heterozygotes. Int. J. Radiat. Biol. 54, 929–943.

Cornu, M., Albert, V., Hall, M.N., 2013. mTOR in aging, metabolism, and cancer. Curr. Opin. Genet. Dev. 23, 53–62.
Cosentino, C., Grieco, D., Costanzo, V., 2011. ATM activates the pentose phosphate pathway promoting anti-oxidant defence and DNA repair. EMBO J. 30, 546–555.
Crawford, T.O., Mandir, A.S., Lefton-Greif, M.A., Goodman, S.N., Goodman, B.K., Sengul, H., Lederman, H.M., 2000. Quantitative neurologic assessment of ataxia-telangiectasia. Neurology 54, 1505–1509.
Crawford, T.O., 1998. Ataxia telangiectasia. Semin. Pediatr. Neurol. 5, 287–294.
Cremona, C.A., Behrens, A., 2014. ATM signalling and cancer. Oncogene 33, 3351–3360.
d'Almeida, A.K., Cavaciuti, E., Dondon, M.G., Lauge, A., Janin, N., Stoppa-Lyonnet, D., Andrieu, N., 2005. Increased risk of breast cancer among female relatives of patients with ataxia-telangiectasia: a causal relationship? Br. J. Cancer 93, 730–732 (author reply 732).
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. Therapy J. Am. Soc. Gene Therapy 21, 42–48.
Daniel, L.L., Daniels, C.R., Harirforoosh, S., Foster, C.R., Singh, M., Singh, K., 2014. Deficiency of ataxia telangiectasia mutated kinase delays inflammatory response in the heart following myocardial infarction. J. Am. Heart Assoc. 3, e001286.
Davis, A.J., Chen, B.P., Chen, D.J., 2014. DNA-PK: a dynamic enzyme in a versatile DSB repair pathway. DNA Repair 17, 21–29.
Demaria, M., Ohtani, N., Youssef, S.A., Rodier, F., Toussaint, W., Mitchell, J.R., Laberge, R.M., Vijg, J., Van Steeg, H., Dolle, M.E., Hoeijmakers, J.H., de Bruin, A., Hara, E., Campisi, J., 2014. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev. Cell 31, 722–733.
Di Mitri, D., Alimonti, A., 2016. Non-Cell-Autonomous regulation of cellular senescence in cancer. Trends Cell Biol. 26, 215–226.
Ditch, S., Paull, T.T., 2012. The ATM protein kinase and cellular redox signaling: beyond the DNA damage response. Trends Biochem. Sci. 37, 15–22.
Doksani, Y., de Lange, T., 2014. The role of double-strand break repair pathways at functional and dysfunctional telomeres. Cold Spring Harb. Perspect. Biol. 6, a016576.
Eaton, J.S., Lin, Z.P., Sartorelli, A.C., Bonawitz, N.D., Shadel, G.S., 2007. Ataxia-telangiectasia mutated kinase regulates ribonucleotide reductase and mitochondrial homeostasis. J. Clin. Invest. 117, 2723–2734.
Edifizi, D., Schumacher, B., 2015. Genome instability in development and aging: insights from nucleotide excision repair in humans, mice, and worms. Biomolecules 5, 1855–1869.
Ehlayel, M., Soliman, A., De Sanctis, V., 2014. Linear growth and endocrine function in children with ataxia telangiectasia. Indian J. Endocrinol. Metab. 18, S93–96.
Errico, A., Costanzo, V., 2012. Mechanisms of replication fork protection: a safeguard for genome stability. Crit. Rev. Biochem. Mol. Biol. 47, 222–235.
Espach, Y., Lochner, A., Strijdom, H., Huisamen, B., 2015. ATM protein kinase signaling, type 2 diabetes and cardiovascular disease. Cardiovasc. Drugs Ther. 29, 51–58.
Exley, A.R., Buckenham, S., Hodges, E., Hallam, R., Byrd, P., Last, J., Trinder, C., Harris, S., Screaton, N., Williams, A.P., Taylor, A.M., Shneerson, J.M., 2011. Premature ageing of the immune system underlies immunodeficiency in ataxia telangiectasia. Clin. Immunol. 140, 26–36.
Falck, J., Coates, J., Jackson, S.P., 2005. Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. Nature 434, 605–611.
Fedier, A., Schlamminger, M., Schwarz, V.A., Haller, U., Howell, S.B., Fink, D., 2003. Loss of atm sensitises p53-deficient cells to topoisomerase poisons and antimetabolites. Ann. Oncol. 14, 938–945.
Feltes, B.C., de Faria Poloni, J., Bonatto, D., 2015. Development and aging: two opposite but complementary phenomena. Interdiscip. Top. Gerontol. 40, 74–84.
Fernet, M., Moullan, N., Lauge, A., Stoppa-Lyonnet, D., Hall, J., 2004. Cellular responses to ionising radiation of AT heterozygotes: differences between missense and truncating mutation carriers. Br. J. Cancer 90, 866–873.
Foster, C.R., Singh, M., Subramanian, V., Singh, K., 2011. Ataxia telangiectasia mutated kinase plays a protective role in beta-adrenergic receptor-stimulated cardiac myocyte apoptosis and myocardial remodeling. Mol. Cell. Biochem. 353, 13–22.
Foster, C.R., Zha, Q., Daniel, L.L., Singh, M., Singh, K., 2012. Lack of ataxia telangiectasia mutated kinase induces structural and functional changes in the heart: role in beta-adrenergic receptor-stimulated apoptosis. Exp. Physiol. 97, 506–515.
Foster, C.R., Daniel, L.L., Daniels, C.R., Dalal, S., Singh, M., Singh, K., 2013. Deficiency of ataxia telangiectasia mutated kinase modulates cardiac remodeling following myocardial infarction: involvement in fibrosis and apoptosis. PLoS One 8, e83513.
Franzke, B., Neubauer, O., Wagner, K.H., 2015. Super DNAging-New insights into DNA integrity, genome stability and telomeres in the oldest old. Mutat. Res. Rev. Mutat. Res. 766, 48–57.
Fu, X., Wan, S., Lyu, Y.L., Liu, L.F., Qi, H., 2008. Etoposide induces ATM-dependent mitochondrial biogenesis through AMPK activation. PLoS One 3, e2009.
Gage, B.M., Alroy, D., Shin, C.Y., Ponomareva, O.N., Dhar, S., Sharma, G.G., Pandita, T.K., Thayer, M.J., Turker, M.S., 2001. Spontaneously immortalized cell lines obtained from adult Atm null mice retain sensitivity to ionizing radiation and exhibit a mutational pattern suggestive of oxidative stress. Oncogene 20, 4291–4297.
Gatei, M., Shkedy, D., Khanna, K.K., Uziel, T., Shiloh, Y., Pandita, T.K., Lavin, M.F., Rotman, G., 2001. Ataxia-telangiectasia: chronic activation of damage-responsive functions is reduced by alpha-lipoic acid. Oncogene 20, 289–294.
Gatti, R.A., Vinters, H.V., 1985. Cerebellar pathology in ataxia-telangiectasia: the significance of basket cells. Kroc Found. Ser. 19, 225–232.
Gatti, R.A., Bick, M., Tam, C.F., Medici, M.A., Oxelius, V.A., Holland, M., Goldstein, A.L., Boder, E., 1982. Ataxia-Telangiectasia: a multiparameter analysis of eight families. Clin. Immunol. Immunopathol. 23, 501–516.
Gatti, R.A., Berkel, I., Boder, E., Braedt, G., Charmley, P., Concannon, P., Ersoy, F., Foroud, T., Jaspers, N.G., Lange, K., et al., 1988. Localization of an ataxia-telangiectasia gene to chromosome 11q22-23. Nature 336, 577–580.
Gatti, R.A., 1995. Ataxia-telangiectasia. Dermatol. Clin. 13, 1–6.
Gilad, S., Khosravi, R., Shkedy, D., Uziel, T., Ziv, Y., Savitsky, K., Rotman, G., Smith, S., Chessa, L., Jorgensen, T.J., Harnik, R., Frydman, M., Sanal, O., Portnoi, S., Goldwicz, Z., Jaspers, N.G., Gatti, R.A., Lenoir, G., Lavin, M.F., Tatsumi, K., Wegner, R.D., Shiloh, Y., Bar-Shira, A., 1996. Predominance of null mutations in ataxia-telangiectasia. Hum. Mol. Genet. 5, 433–439.
Gilad, S., Chessa, L., Khosravi, R., Russell, P., Galanty, Y., Piane, M., Gatti, R.A., Jorgensen, T.J., Shiloh, Y., Bar-Shira, A., 1998. Genotype-phenotype relationships in ataxia-telangiectasia and variants. Am. J. Hum. Genet. 62, 551–561.
Gobbini, E., Cesena, D., Galbiati, A., Lockhart, A., Longhese, M.P., 2013. Interplays between ATM/Tel1 and ATR/Mec1 in sensing and signaling DNA double-strand breaks. DNA Repair 12, 791–799.
Goetz, E.M., Shankar, B., Zou, Y., Morales, J.C., Luo, X., Araki, S., Bachoo, R., Mayo, L.D., Boothman, D.A., 2011. ATM-dependent IGF-1 induction regulates secretory clusterin expression after DNA damage and in genetic instability. Oncogene 30, 3745–3754.
Goldgar, D.E., Healey, S., Dowty, J.G., Da Silva, L., Chen, X., Spurdle, A.B., Terry, M.B., Daly, M.J., Buys, S.M., Southey, M.C., Andrulis, I., John, E.M., Bcfr kConFab Khanna, K.K., Hopper, J.L., Oefner, P.J., Lakhani, S., Chenevix-Trench, G., 2011. Rare variants in the ATM gene and risk of breast cancer. Breast Cancer Res. 13, R73.
Goldsmith, T.C., 2012. On the programmed/non-programmed aging controversy. Biochemistry (Moscow) 77, 729–732.
Goodarzi, A.A., Jeggo, P.A., 2013. The repair and signaling responses to DNA double-strand breaks. Adv. Genet. 82, 1–45.
Gorbunova, V., Seluanov, A., 2016. DNA double strand break repair, aging and the chromatin connection. Mutat. Res. (in press).
Gotoff, S.P., Amirmokri, E., Liebner, E.J., 1967. Ataxia telangiectasia. Neoplasia untoward response to x-irradiation, and tuberous sclerosis. Am. J. Dis. Child. 114, 617–625.
Greenberger, S., Berkun, Y., Ben-Zeev, B., Levi, Y.B., Barziliai, A., Nissenkorn, A., 2013. Dermatologic manifestations of ataxia-telangiectasia syndrome. J. Am. Acad. Dermatol. 68, 932–936.
Gregg, S.Q., Robinson, A.R., Niedernhofer, L.J., 2011. Physiological consequences of defects in ERCC1-XPF DNA repair endonuclease. DNA Repair (Amst.) 10, 781–791.
Guleria, A., Chandna, S., 2015. ATM kinase: much more than a DNA damage responsive protein. DNA Repair 39, 1–120.
Guo, Z., Deshpande, R., Paull, T.T., 2010a. ATM activation in the presence of oxidative stress. Cell Cycle 9, 4805–4811.
Guo, Z., Kozlov, S., Lavin, M.F., Person, M.D., Paull, T.T., 2010b. ATM activation by oxidative stress. Science 330, 517–521.
Gurkar, A.U., Niedernhofer, L.J., 2015. Comparison of mice with accelerated aging caused by distinct mechanisms. Exp. Gerontol. 68, 43–50.
Halaby, M.J., Hibma, J.C., He, J., Yang, D.Q., 2008. ATM protein kinase mediates full activation of Akt and regulates glucose transporter 4 translocation by insulin in muscle cells. Cell. Signal. 20, 1555–1563.
Hannan, M.A., Hellani, A., Al-Khodairy, F.M., Kunhi, M., Siddiqui, Y., Al-Yussef, N., Pangue-Cruz, N., Siewertsen, M., Al-Ahdal, M.N., Aboussekhra, A., 2002. Deficiency in the repair of UV-induced DNA damage in human skin fibroblasts compromised for the ATM gene. Carcinogenesis 23, 1617–1624.
Hartlova, A., Erttmann, S.F., Raffi, F.A., Schmalz, A.M., Resch, U., Anugula, S., Lienenklaus, S., Nilsson, L.M., Kroger, A., Nilsson, J.A., Ek, T., Weiss, S., Gekara, N.O., 2015. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. Immunity 42, 332–343.
Henderson, E.E., Ribecky, R., 1980. DNA repair in lymphoblastoid cell lines established from human genetic disorders. Chem. Biol. Interact. 33, 63–81.
Heppell, A., Butterworth, S.V., Hollis, R.J., Kennaugh, A.A., Beatty, D.W., Taylor, A.M., 1988. Breakage of the T cell receptor alpha chain locus in non malignant clones from patients with ataxia telangiectasia. Hum. Genet. 79, 360–364.
Herrup, K., Li, J., Chen, J., 2013. The role of ATM and DNA damage in neurons: upstream and downstream connections. DNA Repair 12, 600–604.
Herrup, K., 2013. ATM and the epigenetics of the neuronal genome. Mech. Ageing Dev. 134, 434–439.
Hoar, D.I., Sargent, P., 1976. Chemical mutagen hypersensitivity in ataxia telangiectasia. Nature 261, 590–592.
Hoche, F., Seidel, K., Theis, M., Vlaho, S., Schubert, R., Zielen, S., Kieslich, M., 2012. Neurodegeneration in ataxia telangiectasia: what is new? What is evident? Neuropediatrics 43, 119–129.
Jasin, M., Rothstein, R., 2013. Repair of strand Breaks by homologous recombination. Cold Spring Harb. Perspect. Biol. 5, a02740.

Jaspers, N.G., de Wit, J., Regulski, M.R., Bootsma, D., 1982. Abnormal regulation of DNA replication and increased lethality in ataxia telangiectasia cells exposed to carcinogenic agents. Cancer Res. 42, 335–341.
Jenny, N.S., 2012. Inflammation in aging: cause, effect, or both? Discov. Med. 13, 451–460.
Jeong, I., Patel, A.Y., Zhang, Z., Patil, P.B., Nadella, S.T., Nair, S., Ralston, L., Hoormann, J.K., Fisher, J.S., 2010. Role of ataxia telangiectasia mutated in insulin signalling of muscle-derived cell lines and mouse soleus. Acta Physiol. (Oxf.) 198, 465–475.
Jette, N., Lees-Miller, S.P., 2015. The DNA-dependent protein kinase: a multifunctional protein kinase with roles in DNA double strand break repair and mitosis. Prog. Biophys. Mol. Biol. 117, 194–205.
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, 3520–3536.
Jones, D.P., 2015. Redox theory of aging. Redox Biol. 5, 71–79.
Kaidi, A., Jackson, S.P., 2013. KAT5 tyrosine phosphorylation couples chromatin sensing to ATM signalling. Nature 498, 70–74.
Kamsler, A., Daily, D., Hochman, A., Stern, N., Shiloh, Y., Rotman, G., Barzilai, A., 2001. Increased oxidative stress in ataxia telangiectasia evidenced by alterations in redox state of brains from Atm-deficient mice. Cancer Res. 61, 1849–1854.
Kang, C., Xu, Q., Martin, T.D., Li, M.Z., Demaria, M., Aron, L., Lu, T., Yankner, B.A., Campisi, J., Elledge, S.J., 2015. The DNA damage response induces inflammation and senescence by inhibiting autophagy of GATA4. Science 349, aaa5612.
Katyal, S., Lee, Y., Nitiss, K.C., Downing, S.M., Li, Y., Shimada, M., Zhao, J., Russell, H.R., Petrini, J.H., Nitiss, J.L., McKinnon, P.J., 2014. Aberrant topoisomerase-1 DNA lesions are pathogenic in neurodegenerative genome instability syndromes. Nat. Neurosci. 17, 813–821.
Kennaugh, A.A., Butterworth, S.V., Hollis, R., Baer, R., Rabbitts, T.H., Taylor, A.M., 1986. The chromosome breakpoint at 14q32 in an ataxia telangiectasia t(14;14) T cell clone is different from the 14q32 breakpoint in Burkitts and an inv(14) T cell lymphoma. Hum. Genet. 73, 254–259.
Kennedy, B.K., Berger, S.L., Brunet, A., Campisi, J., Cuervo, A.M., Epel, E.S., Franceschi, C., Lithgow, G.J., Morimoto, R.I., Pessin, J.E., Rando, T.A., Richardson, A., Schadt, E.E., Wyss-Coray, T., Sierra, F., 2014. Geroscience: linking aging to chronic disease. Cell 159, 709–713.
Kenyon, C., 2011. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. Philos. Trans. R Soc. Lond. B Biol. Sci. 366, 9–16.
Khoronenkova, S.V., Dianov, G.L., 2015. ATM prevents DSB formation by coordinating SSB repair and cell cycle progression. Proc. Natl. Acad. Sci. U.S.A. 112, 3997–4002.
Kim, S., Peterson, S.E., Jasin, M., Keeney, S., 2016. Mechanisms of germ line genome instability. Semin. Cell Dev. Biol. 54, 177–187.
Klement, K., Goodarzi, A.A., 2014. DNA double strand break responses and chromatin alterations within the aging cell. Exp. Cell Res. 329, 42–52.
Kojis, T.L., Gatti, R.A., Sparkes, R.S., 1991. The cytogenetics of ataxia telangiectasia. Cancer Genet. Cytogenet. 56, 143–156.
Kozlov, S.V., Graham, M.E., Peng, C., Chen, P., Robinson, P.J., Lavin, M.F., 2006. Involvement of novel autophosphorylation sites in ATM activation. EMBO J. 25, 3504–3514.
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.: MCP 54, 177–187, 15, 1032–1047.
Kruger, A., Ralser, M., 2011. ATM is a redox sensor linking genome stability and carbon metabolism. Sci. Signal. 4, pe17.
Lange, J., Pan, J., Cole, F., Thelen, M.P., Jasin, M., Keeney, S., 2011. ATM controls meiotic double-strand-break formation. Nature 479, 237–240.
Lasry, A., Ben-Neriah, Y., 2015. Senescence-associated inflammatory responses: aging and cancer perspectives. Trends Immunol. 36, 217–228.
Lavin, M.F., 2008. Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signalling and cancer. Nature reviews. Mol. Cell Biol. 9, 759–769.
Lee, S.A., Dritschilo, A., Jung, M., 2001. Role of ATM in oxidative stress-mediated c-Jun phosphorylation in response to ionizing radiation and $CdCl_2$. J. Biol. Chem. 276, 11783–11790.
Lee, J.H., Kim, K.H., Morio, T., Kim, H., 2006. Ataxia-telangiectasia-mutated-dependent activation of Ku in human fibroblasts exposed to hydrogen peroxide. Ann. N. Y. Acad. Sci. 1091, 76–82.
Lee, J.H., Guo, Z., Myler, L.R., Zheng, S., Paull, T.T., 2014. Direct activation of ATM by resveratrol under oxidizing conditions. PLoS One 9, e97969.
Lefton-Greif, M.A., Crawford, T.O., Winkelstein, J.A., Loughlin, G.M., Koerner, C.B., Zahurak, M., Lederman, H.M., 2000. Oropharyngeal dysphagia and aspiration in patients with ataxia-telangiectasia. J. Pediatr. 136, 225–231.
Leonard, J.C., Mullinger, A.M., Schmidt, J., Cordell, H.J., Johnson, R.T., 2004. Genome instability in ataxia telangiectasia (A-T) families: camptothecin-induced damage to replicating DNA discriminates between obligate A-T heterozygotes, A-T homozygotes and controls. Biosci. Rep. 24, 617–629.
Li, J., Chen, J., Ricupero, C.L., Hart, R.P., Schwartz, M.S., Kusnecov, A., Herrup, K., 2012. Nuclear accumulation of HDAC4 in ATM deficiency promotes neurodegeneration in ataxia telangiectasia. Nat. Med. 18, 783–790.
Li, J., Hart, R.P., Mallimo, E.M., Swerdel, M.R., Kusnecov, A.W., Herrup, K., 2013. EZH2-mediated H3K27 trimethylation mediates neurodegeneration in ataxia-telangiectasia. Nat. Neurosci. 16, 1745–1753.
Lin, D.D., Barker, P.B., Lederman, H.M., Crawford, T.O., 2014. Cerebral abnormalities in adults with ataxia-telangiectasia. Am. J. Neuroradiol. 35, 119–123.
Liu, N., Stoica, G., Yan, M., Scofield, V.L., Qiang, W., Lynn, W.S., Wong, P.K., 2005. ATM deficiency induces oxidative stress and endoplasmic reticulum stress in astrocytes. Lab. Invest. J. Tech. Methods Pathol. 85, 1471–1480.
Loaiza, N., Demaria, M., 2016. Cellular senescence and tumor promotion: is aging the key? Biochim. Biophys. Acta 1865, 155–167.
Loeb, D.M., Lederman, H.M., Winkelstein, J.A., 2000. Lymphoid malignancy as a presenting sign of ataxia-telangiectasia. J. Pediatr. Hematol. Oncol. 22, 464–467.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Lovejoy, C.A., Cortez, D., 2009. Common mechanisms of PIKK regulation. DNA Repair 8, 1004–1008.
Ludwig, L.B., Valiati, V.H., Palazzo, R.P., Jardim, L.B., da Rosa, D.P., Bona, S., Rodrigues, G., Marroni, N.P., Pra, D., Maluf, S.W., 2013. Chromosome instability and oxidative stress markers in patients with ataxia telangiectasia and their parents. Biomed. Res. Int. 2013, 762048.
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, e99983.
Marechal, A., Zou, L., 2013. DNA damage sensing by the ATM and ATR kinases. Cold Spring Harb. Perspect. Biol. 5.
Maslov, A.Y., Ganapathi, S., Westerhof, M., Quispe-Tintaya, W., White, R.R., Van Houten, B., Reiling, E., Dollé, M.E., van Steeg, H., Hasty, P., Hoeijmakers, J.H., Vijg, J., 2013. DNA damage in normally and prematurely aged mice. Aging Cell 12, 467–477.
Matsuoka, S., Ballif, B.A., Smogorzewska, A., McDonald 3rd, E.R., Hurov, K.E., Luo, J., Bakalarski, C.E., Zhao, Z., Solimini, N., Lerenthal, Y., Shiloh, Y., Gygi, S.P., Elledge, S.J., 2007. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science 316, 1160–1166.
Maynard, S., Fang, E.F., Scheibye-Knudsen, M., Croteau, D.L., Bohr, V.A., 2015. DNA damage, DNA, repair, aging, and neurodegeneration. Cold Spring Harb. Perspect. Med. 5.
McDonald, C.J., Ostini, L., Wallace, D.F., John, A.N., Watters, D.J., Subramaniam, V.N., 2011. Iron loading and oxidative stress in the Atm-/- mouse liver. Am. J. Physiol. Gastrointest. Liver Physiol. 300, G554–560.
McGrath-Morrow, S.A., Collaco, J.M., Detrick, B., Lederman, H.M., 2016. Serum interleukin-6 levels and pulmonary function in ataxia-Telangiectasia. J. Pediatr. 171, 256–261.
McKinnon, P.J., 2012. ATM and the molecular pathogenesis of ataxia telangiectasia. Annu. Rev. Pathol. 7, 303–321.
Meneret, A., Ahmar-Beaugendre, Y., Rieunier, G., Mahlaoui, N., Gaymard, B., Apartis, E., Tranchant, C., Rivaud-Pechoux, S., Degos, B., Benyahia, B., Suarez, F., Maisonobe, T., Koenig, M., Durr, A., Stern, M.H., Dubois d'Enghien, C., Fischer, A., Vidailhet, M., Stoppa-Lyonnet, D., Grabli, D., Anheim, M., 2014. The pleiotropic movement disorders phenotype of adult ataxia-telangiectasia. Neurology 83, 1087–1095.
Mercer, J.R., Cheng, K.K., Figg, N., Gorenne, I., Mahmoudi, M., Griffin, J., Vidal-Puig, A., Logan, A., Murphy, M.P., Bennett, M., 2010. DNA damage links mitochondrial dysfunction to atherosclerosis and the metabolic syndrome. Circ. Res. 107, 1021–1031.
Mercer, J.R., Yu, E., Figg, N., Cheng, K.K., Prime, T.A., Griffin, J.L., Masoodi, M., Vidal-Puig, A., Murphy, M.P., Bennett, M.R., 2012. The mitochondria-targeted antioxidant MitoQ decreases features of the metabolic syndrome in ATM+/−/ApoE-/- mice. Free Rad. Biol. Med. 52, 841–849.
Metcalfe, J.A., Parkhill, J., Campbell, L., Stacey, M., Biggs, P., Byrd, P.J., Taylor, A.M., 1996. Accelerated telomere shortening in ataxia telangiectasia. Nat. Genet. 13, 350–353.
Miles, P.D., Treuner, K., Latronica, M., Olefsky, J.M., Barlow, C., 2007. Impaired insulin secretion in a mouse model of ataxia telangiectasia. Am. J. Physiol. Endocrinol. Metab. 293, E70–74.
Mirzayans, R., Smith, B.P., Paterson, M.C., 1989. Hypersensitivity to cell killing and faulty repair of 1-beta-D-arabinofuranosylcytosine-detectable sites in human (ataxia-telangiectasia) fibroblasts treated with 4-nitroquinoline 1-oxide. Cancer Res. 49, 5523–5529.
Morgan, J.L., Holcomb, T.M., Morrissey, R.W., 1968. Radiation reaction in ataxia telangiectasia. Am. J. Dis. Child. 116, 557–558.
Morrell, D., Chase, C.L., Kupper, L.L., Swift, M., 1986. Diabetes mellitus in ataxia-telangiectasia, Fanconi anemia, xeroderma pigmentosum, common variable immune deficiency, and severe combined immune deficiency families. Diabetes 35, 143–147.
Mu, J.J., Wang, Y., Luo, H., Leng, M., Zhang, J., Yang, T., Besusso, D., Jung, S.Y., Qin, J., 2007. A proteomic analysis of ataxia telangiectasia-mutated (ATM)/ATM-Rad3-related (ATR) substrates identifies the ubiquitin-proteasome system as a regulator for DNA damage checkpoints. J. Biol. Chem. 282, 17330–17334.
Muñoz-Espín, D., Serrano, M., 2014. Cellular senescence: from physiology to pathology. Nat. Rev. Mol. Cell Biol. 15, 482–496.
Munoz-Espin, D., Serrano, M., 2014. Cellular senescence: from physiology to pathology. Nature reviews. Mol. Cell Biol. 15, 482–496.
Murphy, R.C., Berdon, W.E., Ruzal-Shapiro, C., Hall, E.J., Kornecki, A., Daneman, A., Brunelle, F., Campbell, J.B., 1999. Malignancies in pediatric patients with ataxia telangiectasia. Pediatr. Radiol. 29, 225–230.
Naka, K., Tachibana, A., Ikeda, K., Motoyama, N., 2004. Stress-induced premature senescence in hTERT-expressing ataxia telangiectasia fibroblasts. J. Biol. Chem. 279, 2030–2037.

Nakamura, K., Fike, F., Haghayegh, S., Saunders-Pullman, R., Dawson, A.J., Dork, T., Gatti, R.A., 2014. A-TWinnipeg: pathogenesis of rare ATM missense mutation c.6200C > A with decreased protein expression and downstream signaling early-onset dystonia, cancer, and life-threatening radiotoxicity. Mol. Genet. Genom. Med. 2, 332–340.
Neubauer, S., Arutyunyan, R., Stumm, M., Dork, T., Bendix, R., Bremer, M., Varon, R., Sauer, R., Gebhart, E., 2002. Radiosensitivity of ataxia telangiectasia and Nijmegen breakage syndrome homozygotes and heterozygotes as determined by three-color FISH chromosome painting. Radiat. Res. 157, 312–321.
Nissenkorn, A., Ben-Zeev, B., 2015. Ataxia telangiectasia. Handb Clin Neurol 132, 199–214.
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. Pediatr. Res.
Nowak-Wegrzyn, A., Crawford, T.O., Winkelstein, J.A., Carson, K.A., Lederman, H.M., 2004. Immunodeficiency and infections in ataxia-telangiectasia. J. Pediatr. 144, 505–511.
Olsen, J.H., Hahnemann, J.M., Borresen-Dale, A.L., Brondum-Nielsen, K., Hammarstrom, L., Kleinerman, R., Kaariainen, H., Lonnqvist, T., Sankila, R., Seersholm, N., Tretli, S., Yuen, J., Boice Jr., J.D., Tucker, M., 2001. Cancer in patients with ataxia-telangiectasia and in their relatives in the nordic countries. J. Natl. Cancer Inst. 93, 121–127.
Ovadya, Y., Krizhanovsky, V., 2014. Senescent cells: sASPected drivers of age-related pathologies. Biogerontology 15, 627–642.
Paglia, L.L., Lauge, A., Weber, J., Champ, J., Cavaciuti, E., Russo, A., Viovy, J.L., Stoppa-Lyonnet, D., 2010. ATM germline mutations in women with familial breast cancer and a relative with haematological malignancy. Breast Cancer Res. Treat. 119, 443–452.
Pandita, T.K., Pathak, S., Geard, C.R., 1995. Chromosome end associations, telomeres and telomerase activity in ataxia telangiectasia cells. Cytogenet. Cell Genet. 71, 86–93.
Panier, S., Durocher, D., 2013. Push back to respond better: regulatory inhibition of the DNA double-strand break response. Nature reviews. Cancer 13, 661–672.
Parshad, R., Sanford, K.K., Jones, G.M., Tarone, R.E., 1985. G2 chromosomal radiosensitivity of ataxia-telangiectasia heterozygotes. Cancer Genet. Cytogenet. 14, 163–168.
Paterson, M.C., Smith, B.P., Lohman, P.H., Anderson, A.K., Fishman, L., 1976. Defective excision repair of gamma-ray-damaged DNA in human (ataxia telangiectasia) fibroblasts. Nature 260, 444–447.
Paull, T.T., 2015. Mechanisms of ATM activation. Annu. Rev. Biochem. 84, 711–738.
Peretz, S., Jensen, R., Baserga, R., Glazer, P.M., 2001. ATM-dependent expression of the insulin-like growth factor-I receptor in a pathway regulating radiation response. Proc. Natl. Acad. Sci. U. S. A. 98, 1676–1681.
Perlman, S.L., Boder Deceased, E., Sedgewick, R.P., Gatti, R.A., 2012. Ataxia-telangiectasia. Handb. Clin. Neurol. 103, 307–332.
Pernin, D., Bay, J.O., Uhrhammer, N., Bignon, Y.J., 1999. ATM heterozygote cells exhibit intermediate levels of apoptosis in response to streptonigrin and etoposide. Eur. J. Cancer 35, 1130–1135.
Piaceri, I., Bagnoli, S., Tedde, A., Sorbi, S., Nacmias, B., 2013. Ataxia-telangiectasia mutated (ATM) genetic variant in Italian centenarians. Neurol. Sci. 34, 573–575.
Pinto, M., Moraes, C.T., 2015. Mechanisms linking mtDNA damage and aging. Free Rad. Biol. Med. 85, 250–258.
Platzer, M., Rotman, G., Bauer, D., Uziel, T., Savitsky, K., Bar-Shira, A., Gilad, S., Shiloh, Y., Rosenthal, A., 1997. Ataxia-telangiectasia locus: sequence analysis of 184 kb of human genomic DNA containing the entire ATM gene. Genome Res. 7, 592–605.
Polo, S.E., Jackson, S.P., 2011. Dynamics of DNA damage response proteins at DNA breaks: a focus on protein modifications. Genes Dev. 25, 409–433.
Pommerening, H., van Dullemen, S., Kieslich, M., Schubert, R., Zielen, S., Voss, S., 2015. Body composition, muscle strength and hormonal status in patients with ataxia telangiectasia: a cohort study. Orphanet J. Rare Dis. 10, 155.
Radhakrishnan, S.K., Jette, N., Lees-Miller, S.P., 2014. Non-homologous end joining: emerging themes and unanswered questions. DNA Repair 17, 2–8.
Rashi-Elkeles, S., Elkon, R., Weizman, N., Linhart, C., Amariglio, N., Sternberg, G., Rechavi, G., Barzilai, A., Shamir, R., Shiloh, Y., 2006. Parallel induction of ATM-dependent pro- and antiapoptotic signals in response to ionizing radiation in murine lymphoid tissue. Oncogene 25, 1584–1592.
Reed, W.B., Epstein, W.L., Boder, E., Sedgwick, R., 1966. Cutaneous manifestations of ataxia-telangiectasia. JAMA 195, 746–753.
Reichenbach, J., Schubert, R., Schindler, D., Muller, K., Bohles, H., Zielen, S., 2002. Elevated oxidative stress in patients with ataxia telangiectasia. Antioxid. Redox Signal. 4, 465–469.
Rein, K., Stracker, T.H., 2014. The MRE11 complex: an important source of stress relief. Exp. Cell Res. 329, 162–169.
Reliene, R., Schiestl, R.H., 2007. Antioxidants suppress lymphoma and increase longevity in Atm-deficient mice. J. Nutr. 137, 229S–232S.
Reliene, R., Fischer, E., Schiestl, R.H., 2004. Effect of N-acetyl cysteine on oxidative DNA damage and the frequency of DNA deletions in atm-deficient mice. Cancer Res. 64, 5148–5153.
Ribezzo, F., Shiloh, Y., Schumacher, B., 2016. Systemic DNA damage responses in aging and diseases. Semin. Cancer Biol. (in press).
Rodier, F., Coppé, J.P., Patil, C.K., Hoeijmakers, W.A., Muñoz, D.P., Raza, S.R., Freund, A., Campeau, E., Davalos, A.R., Campisi, J., 2009. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat. Cell Biol. 11, 973–979.
Rosin, M.P., Ochs, H.D., 1986. In vivo chromosomal instability in ataxia-telangiectasia homozygotes and heterozygotes. Hum. Genet. 74, 335–340.
Rosin, M.P., Ochs, H.D., Gatti, R.A., Boder, E., 1989. Heterogeneity of chromosomal breakage levels in epithelial tissue of ataxia-telangiectasia homozygotes and heterozygotes. Hum. Genet. 83, 133–138.
Rotman, G., Shiloh, Y., 1997a. Ataxia-telangiectasia: is ATM a sensor of oxidative damage and stress? Bioessays 19, 911–917.
Rotman, G., Shiloh, Y., 1997b. The ATM gene and protein: possible roles in genome surveillance, checkpoint controls and cellular defence against oxidative stress. Cancer Surv. 29, 285–304.
Sadighi Akha, A.A., Humphrey, R.L., Winkelstein, J.A., Loeb, D.M., Lederman, H.M., 1999. Oligo-/monoclonal gammopathy and hypergammaglobulinemia in ataxia-telangiectasia: a study of 90 patients. Medicine (Baltimore). 78, 370–381.
Salama, R., Sadaie, M., Hoare, M., Narita, M., 2014. Cellular senescence and its effector programs. Genes Dev. 28, 99–114.
Sandoval, N., Platzer, M., Rosenthal, A., Dork, T., Bendix, R., Skawran, B., Stuhrmann, M., Wegner, R.D., Sperling, K., Banin, S., Shiloh, Y., Baumer, A., Bernthaler, U., Sennefelder, H., Brohm, M., Weber, B.H., Schindler, D., 1999. Characterization of ATM gene mutations in 66 ataxia telangiectasia families. Hum. Mol. Genet. 8, 69–79.
Sanford, K.K., Parshad, R., Price, F.M., Jones, G.M., Tarone, R.E., Eierman, L., Hale, P., Waldmann, T.A., 1990. Enhanced chromatid damage in blood lymphocytes after G2 phase x irradiation, a marker of the ataxia-telangiectasia gene. J. Natl. Cancer Inst. 82, 1050–1054.
Saunders-Pullman, R., Raymond, D., Stoessl, A.J., Hobson, D., Nakamura, K., Pullman, S., Lefton, D., Okun, M.S., Uitti, R., Sachdev, R., Stanley, K., San Luciano, M., Hagenah, J., Gatti, R., Ozelius, L.J., Bressman, S.B., 2012. Variant ataxia-telangiectasia presenting as primary-appearing dystonia in Canadian Mennonites. Neurology 78, 649–657.
Savitsky, K., Bar-Shira, A., Gilad, S., Rotman, G., Ziv, Y., Vanagaite, L., Tagle, D.A., Smith, S., Uziel, T., Sfez, S., Ashkenazi, M., Pecker, I., Frydman, M., Harnik, R., Patanjali, S.R., Simmons, A., Clines, G.A., Sartiel, A., Gatti, R.A., Chessa, L., Sanal, O., Lavin, M.F., Jaspers, N.G., Taylor, A.M., Arlett, C.F., Miki, T., Weissman, S.M., Lovett, M., Collins, F.S., Shiloh, Y., 1995a. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science 268, 1749–1753.
Savitsky, K., Sfez, S., Tagle, D.A., Ziv, Y., Sartiel, A., Collins, F.S., Shiloh, Y., Rotman, G., 1995b. The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulators in different species. Hum. Mol. Genet. 4, 2025–2032.
Schalch, D.S., McFarlin, D.E., Barlow, M.H., 1970. An unusual form of diabetes mellitus in ataxia telangiectasia. N. Engl. J. Med. 282, 1396–1402.
Schieber, M., Chandel, N.S., 2014. ROS function in redox signaling and oxidative stress. Current Biol. CB 24, R453–462.
Schiewer, M.J., Knudsen, K.E., 2016. Linking DNA damage and hormone signaling pathways in cancer. Trends Endocrinol. Metab. 27, 216–225.
Schneider, J.G., Finck, B.N., Ren, J., Standley, K.N., Takagi, M., Maclean, K.H., Bernal-Mizrachi, C., Muslin, A.J., Kastan, M.B., Semenkovich, C.F., 2006. ATM-dependent suppression of stress signaling reduces vascular disease in metabolic syndrome. Cell Metab. 4, 377–389.
Schubert, R., Reichenbach, J., Zielen, S., 2005. Growth factor deficiency in patients with ataxia telangiectasia. Clin. Exp. Immunol. 140, 517–519.
Scott, D., Spreadborough, A.R., Jones, L.A., Roberts, S.A., Moore, C.J., 1996. Chromosomal radiosensitivity in G2-phase lymphocytes as an indicator of cancer predisposition. Radiat. Res. 145, 3–16.
Scudiero, D.A., 1980. Decreased DNA repair synthesis and defective colony-forming ability of ataxia telangiectasia fibroblast cell strains treated with *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Cancer Res. 40, 984–990.
Sedgwick, R.P., Boder, E., 1960. Progressive ataxia in childhood with particular reference to ataxia-telangiectasia. Neurology 10, 705–715.
Segal-Raz, H., Mass, G., Baranes-Bachar, K., Lerenthal, Y., Wang, S.Y., Chung, Y.M., Ziv-Lehrman, S., Strom, C.E., Helleday, T., Hu, M.C., Chen, D.J., Shiloh, Y., 2011. ATM-mediated phosphorylation of polynucleotide kinase/phosphatase is required for effective DNA double-strand break repair. EMBO Rep. 12, 713–719.
Semlitsch, M., Shackelford, R.E., Zirkl, S., Sattler, W., Malle, E., 2011. ATM protects against oxidative stress induced by oxidized low-density lipoprotein. DNA Repair 10, 848–860.
Sergiev, P.V., Dontsova, O.A., Berezkin, G.V., 2015. Theories of aging: an ever-evolving field. Acta Nat. 7, 9–18.
Sharma, N.K., Lebedeva, M., Thomas, T., Kovalenko, O.A., Stumpf, J.D., Shadel, G.S., Santos, J.H., 2014. Intrinsic mitochondrial DNA repair defects in ataxia telangiectasia. DNA Repair 13, 22–31.
Sharpless, N.E., Sherr, C.J., 2015. Forging a signature of in vivo senescence. Nat. Rev. Cancer 15, 397–408.
Shibata, A., Jeggo, P.A., 2014. DNA double-strand break repair in a cellular context. Clin. Oncol. 26, 243–249.
Shigeta, T., Takagi, M., Delia, D., Chessa, L., Iwata, S., Kanke, Y., Asada, M., Eguchi, M., Mizutani, S., 1999. Defective control of apoptosis and mitotic spindle checkpoint in heterozygous carriers of ATM mutations. Cancer Res. 59, 2602–2607.
Shiloh, Y., Ziv, Y., 2013. The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. Nat. Rev. Mol. Cell Biol. 14, 197–210.
Shiloh, Y., Tabor, E., Becker, Y., 1982a. Cellular hypersensitivity to neocarzinostatin in ataxia-telangiectasia skin fibroblasts. Cancer Res. 42, 2247–2249.

Shiloh, Y., Tabor, E., Becker, Y., 1982b. 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, 191–199.
Shiloh, Y., Tabor, E., Becker, Y., 1982c. The response of ataxia-telangiectasia homozygous and heterozygous skin fibroblasts to neocarzinostatin. Carcinogenesis 3, 815–820.
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, 1317–1322.
Shiloh, Y., Tabor, E., Becker, Y., 1985. Cells from patients with ataxia telangiectasia are abnormally sensitive to the cytotoxic effect of a tumor promoter, phorbol-12-myristate-13-acetate. Mutat. Res. 149, 283–286.
Shiloh, Y., Parshad, R., Sanford, K.K., Jones, G.M., 1986. Carrier detection in ataxia-telangiectasia. Lancet 1, 689–690.
Shiloh, Y., Parshad, R., Frydman, M., Sanford, K.K., Portnoi, S., Ziv, Y., Jones, G.M., 1989. G2 chromosomal radiosensitivity in families with ataxia-telangiectasia. Hum. Genet. 84, 15–18.
Shiloh, Y., 2014. ATM: expanding roles as a chief guardian of genome stability. Exp. Cell Res. 329, 154–161.
Silvestri, G., Masciullo, M., Piane, M., Savio, C., Modoni, A., Santoro, M., Chessa, L., 2010. Homozygosity for c 6325T > G transition in the ATM gene causes an atypical, late-onset variant form of ataxia-telangiectasia. J. Neurol. 257, 1738–1740.
Sirbu, B.M., Cortez, D., 2013. DNA damage response: three levels of DNA repair regulation. Cold Spring Harb.Perspect. Biol. 5, a012724.
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, 2659–2665.
Smilenov, L.B., Dhar, S., Pandita, T.K., 1999. Altered telomere nuclear matrix interactions and nucleosomal periodicity in ataxia telangiectasia cells before and after ionizing radiation treatment. Mol. Cell. Biol. 19, 6963–6971.
Smilenov, L.B., Brenner, D.J., Hall, E.J., 2001. Modest increased sensitivity to radiation oncogenesis in ATM heterozygous versus wild-type mammalian cells. Cancer Res. 61, 5710–5713.
Smith, P.J., Paterson, M.C., 1980. Defective DNA repair and increased lethality in ataxia telangiectasia cells exposed to 4-nitroquinoline-1-oxide. Nature 287, 747–749.
Smith, P.J., Makinson, T.A., Watson, J.V., 1989. Enhanced sensitivity to camptothecin in ataxia-telangiectasia cells and its relationship with the expression of DNA topoisomerase I. Int. J. Radiat. Biol. 55, 217–231.
Soresina, A., Meini, A., Lougaris, V., Cattaneo, G., Pellegrino, S., Piane, M., Darra, F., Plebani, A., 2008. Different clinical and immunological presentation of ataxia-telangiectasia within the same family. Neuropediatrics 39, 43–45.
Speit, G., Trenz, K., Schutz, P., Bendix, R., Dork, T., 2000. Mutagen sensitivity of human lymphoblastoid cells with a BRCA1 mutation in comparison to ataxia telangiectasia heterozygote cells. Cytogenet. Cell Genet. 91, 261–266.
Stern, N., Hochman, A., Zemach, N., Weizman, N., Hammel, I., Shiloh, Y., Rotman, G., Barzilai, A., 2002. Accumulation of DNA damage and reduced levels of nicotine adenine dinucleotide in the brains of Atm-deficient mice. J. Biol. Chem. 277, 602–608.
Stewart, G.S., Maser, R.S., Stankovic, T., Bressan, D.A., Kaplan, M.I., Jaspers, N.G., Raams, A., Byrd, P.J., Petrini, J.H., Taylor, A.M., 1999. The DNA double-strand break repair gene hMRE11 is mutated in individuals with an ataxia-telangiectasia-like disorder. Cell 99, 577–587.
Stracker, T.H., Petrini, J.H., 2011. The MRE11 complex: starting from the ends. Nat. Rev. Mol. Cell Biol. 12, 90–103.
Su, Y., Swift, M., 2000. Mortality rates among carriers of ataxia-telangiectasia mutant alleles. Ann. Intern. Med. 133, 770–778.
Sun, Y., Xu, Y., Roy, K., Price, B.D., 2007. DNA damage-induced acetylation of lysine 3016 of ATM activates ATM kinase activity. Mol. Cell. Biol. 27, 8502–8509.
Swift, M., Chase, C., 1983. Cancer and cardiac deaths in obligatory ataxia-telangiectasia heterozygotes. Lancet 1, 1049–1050.
Swift, M., Lukin, J.L., 2008. Breast cancer incidence and the effect of cigarette smoking in heterozygous carriers of mutations in the ataxia-telangiectasia gene. Cancer Epidemiol. Biomark. Prev. 17, 3188–3192.
Swift, M., Morrell, D., Cromartie, E., Chamberlin, A.R., Skolnick, M.H., Bishop, D.T., 1986. The incidence and gene frequency of ataxia-telangiectasia in the United States. Am. J. Hum. Genet. 39, 573–583.
Swift, M., Chase, C.L., Morrell, D., 1990. Cancer predisposition of ataxia-telangiectasia heterozygotes. Cancer Genet. Cytogenet. 46, 21–27.
Takai, S., Sanford, K.K., Tarone, R.E., 1990. A procedure for carrier detection in ataxia-telangiectasia. Cancer Genet. Cytogenet. 46, 139–140.
Takao, N., Li, Y., Yamamoto, K., 2000. Protective roles for ATM in cellular response to oxidative stress. FEBS Lett. 472, 133–136.
Taylor, A.M., Butterworth, S.V., 1986. Clonal evolution of T-cell chronic lymphocytic leukaemia in a patient with ataxia telangiectasia. J. Int. Cancer 37, 511–516.
Taylor, A.M., Edwards, M.J., 1982. Malignancy, DNA damage and chromosomal aberrations in ataxia telangiectasia. IARC Sci. Publ., 119–126.
Taylor, A.M., Harnden, D.G., Arlett, C.F., Harcourt, S.A., Lehmann, A.R., Stevens, S., Bridges, B.A., 1975. Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. Nature 258, 427–429.
Taylor, A.M., Rosney, C.M., Campbell, J.B., 1979. Unusual sensitivity of ataxia telangiectasia cells to bleomycin. Cancer Res. 39, 1046–1050.
Taylor, A.M., Groom, A., Byrd, P.J., 2004. Ataxia-telangiectasia-like disorder (ATLD)-its clinical presentation and molecular basis. DNA Repair 3, 1219–1225.
Taylor, A.M., Lam, Z., Last, J.I., Byrd, P.J., 2014. Ataxia telangiectasia: more variation at clinical and cellular levels. Clin. Genet. 87, 199–208.
Taylor, A.M., Lam, Z., Last, J.I., Byrd, P.J., 2015. Ataxia telangiectasia: more variation at clinical and cellular levels. Clin. Genet. 87, 199–208.
Taylor, A.M., 1978. Unrepaired DNA strand breaks in irradiated ataxia telangiectasia lymphocytes suggested from cytogenetic observations. Mutat. Res. 50, 407–418.
Teo, I.A., Arlett, C.F., 1982. The response of a variety of human fibroblast cell strains to the lethal effects of alkylating agents. Carcinogenesis 3, 33–37.
Thompson, D., Duedal, S., Kirner, J., McGuffog, L., Last, J., Reiman, A., Byrd, P., Taylor, M., Easton, D.F., 2005. Cancer risks and mortality in heterozygous ATM mutation carriers. J. Natl. Cancer Inst. 97, 813–822.
Thompson, L.H., 2012. Recognition, signaling, and repair of DNA double-strand breaks produced by ionizing radiation in mammalian cells: the molecular choreography. Mutat. Res. 751, 158–246.
Till, A., Lakhani, R., Burnett, S.F., Subramani, S., 2012. Pexophagy: the selective degradation of peroxisomes. Int. J. Cell Biol. 2012, 512721.
Tripathi, D.N., Walker, C.L., 2016. The peroxisome as a cell signaling organelle. Curr. Opin. Cell Biol. 39, 109–112.
Tripathi, D.N., Chowdhury, R., Trudel, L.J., Tee, A.R., Slack, R.S., Walker, C.L., Wogan, G.N., 2013. Reactive nitrogen species regulate autophagy through ATM-AMPK-TSC2-mediated suppression of mTORC1. Proc. Natl. Acad. Sci. U. S. A. 110, E2950–2957.
Uziel, T., Savitsky, K., Platzer, M., Ziv, Y., Helbitz, T., Nehls, M., Boehm, T., Rosenthal, A., Shiloh, Y., Rotman, G., 1996. Genomic organization of the ATM gene. Genomics 33, 317–320.
Uziel, T., Lerenthal, Y., Moyal, L., Andegeko, Y., Mittelman, L., Shiloh, Y., 2003. Requirement of the MRN complex for ATM activation by DNA damage. EMBO J. 22, 5612–5621.
van Deursen, J.M., 2014. The role of senescent cells in ageing. Nature 509, 439–446.
van Os, N.J., Roeleveld, N., Weemaes, C.M., Jongmans, M.C., Janssens, G.O., Taylor, A.M., Hoogerbrugge, N., Willemsen, M.A., 2016. Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, Meta-analysis and evidence-based guideline. Clin. Genet. (in press).
Valentin-Vega, Y.A., Kastan, M.B., 2012. A new role for ATM: regulating mitochondrial function and mitophagy. Autophagy 8, 840–841.
Valentin-Vega, Y.A., Maclean, K.H., Tait-Mulder, J., Milasta, S., Steeves, M., Dorsey, F.C., Cleveland, J.L., Green, D.R., Kastan, M.B., 2012. Mitochondrial dysfunction in ataxia-telangiectasia. Blood 119, 1490–1500.
Varghese, S., Schmidt-Ullrich, R.K., Dritschilo, A., Jung, M., 1999. Enhanced radiation late effects and cellular radiation sensitivity in an ATM heterozygous breast cancer patient. Radiat. Oncol. Investig. 7, 231–237.
Vaziri, H., 1997. Critical telomere shortening regulated by the ataxia-telangiectasia gene acts as a DNA damage signal leading to activation of p53 protein and limited life-span of human diploid fibroblasts. A review. Biochem. Biokhimiia 62, 1306–1310.
Velarde, M.C., Demaria, M., Campisi, J., 2013. Senescent cells and their secretory phenotype as targets for cancer therapy. Interdiscip. Top. Gerontol. 38, 17–27.
Verhagen, M.M., Abdo, W.F., Willemsen, M.A., Hogervorst, F.B., Smeets, D.F., Hiel, J.A., Brunt, E.R., van Rijn, M.A., Majoor Krakauer, D., Oldenburg, R.A., Broeks, A., Last, J.I., van't Veer, L.J., Tijssen, M.A., Dubois, A.M., Kremer, H.P., Weemaes, C.M., Taylor, A.M., van Deuren, M., 2009. Clinical spectrum of ataxia-telangiectasia in adulthood. Neurology 73, 430–437.
Verhagen, M.M., Last, J.I., Hogervorst, F.B., Smeets, D.F., Roeleveld, N., Verheijen, F., Catsman-Berrevoets, C.E., Wulffraat, N.M., Cobben, J.M., Hiel, J., Brunt, E.R., Peeters, E.A., Gomez Garcia, E.B., van der Knaap, M.S., Lincke, C.R., Laan, L.A., Tijssen, M.A., van Rijn, M.A., Majoor-Krakauer, D., Visser, M., van 't Veer, L.J., Kleijer, W.J., van de Warrenburg, B.P., Warris, A., de Groot, I.J., de Groot, R., Broeks, A., Preijers, F., Kremer, B.H., Weemaes, C.M., Taylor, M.A., van Deuren, M., Willemsen, M.A., 2012a. Presence of ATM protein and residual kinase activity correlates with the phenotype in ataxia-telangiectasia: a genotype-phenotype study. Hum. Mutat. 33, 561–571.
Verhagen, M.M., Martin, J.J., van Deuren, M., Ceuterick-de Groote, C., Weemaes, C.M., Kremer, B.H., Taylor, M.A., Willemsen, M.A., Lammens, M., 2012b. Neuropathology in classical and variant ataxia-telangiectasia. Neuropathology 32, 234–244.
Vermeij, W.P., Hoeijmakers, J.H., Pothof, J., 2014. Aging: not all DNA damage is equal. Curr. Opin. Genet. Dev. 26C, 124–130.
Vermeij, W.P., Hoeijmakers, J.H., Pothof, J., 2016. Genome integrity in aging: human syndromes, mouse models, and therapeutic options. Annu. Rev. Pharmacol. Toxicol. 56, 427–445.
Vijg, J., Campisi, J., 2008. Puzzles, promises and a cure for ageing. Nature 454, 1065–1071.
Vijg, J., Suh, Y., 2013. Genome instability and aging. Annu. Rev. Physiol. 75, 645–668.
Viniegra, J.G., Martinez, N., Modirassari, P., Hernandez Losa, J., Parada Cobo, C., Sanchez-Arevalo Lobo, V.J., Aceves Luquero, C.I., Alvarez-Vallina, L., Ramon y Cajal, S., Rojas, J.M., Sanchez-Prieto, R., 2005. Full activation of PKB/Akt in response to insulin or ionizing radiation is mediated through ATM. J. Biol. Chem. 280, 4029–4036.
Vinters, H.V., Gatti, R.A., Rakic, P., 1985. Sequence of cellular events in cerebellar ontogeny relevant to expression of neuronal abnormalities in ataxia-telangiectasia. Kroc Found. Ser. 19, 233–255.
Voss, S., Pietzner, J., Hoche, F., Taylor, A.M., Last, J.I., Schubert, R., Zielen, S., 2014. Growth retardation and growth hormone deficiency in patients with Ataxia telangiectasia. Growth Factors 32, 123–129.

Wallace, S.S., 2014. Base excision repair: a critical player in many games. DNA Repair 19, 14–26.
Ward, A.J., Olive, P.L., Burr, A.H., Rosin, M.P., 1994. Response of fibroblast cultures from ataxia-telangiectasia patients to reactive oxygen species generated during inflammatory reactions. Environ. Mol. Mutagen. 24, 103–111.
Watters, D., Kedar, P., Spring, K., Bjorkman, J., Chen, P., Gatei, M., Birrell, G., Garrone, B., Srinivasa, P., Crane, D.I., Lavin, M.F., 1999. Localization of a portion of extranuclear ATM to peroxisomes. J. Biol. Chem. 274, 34277–34282.
Watters, D.J., 2003. Oxidative stress in ataxia telangiectasia. Redox Repo. Commun. Free Radic. Res. 8, 23–29.
Weaver, M., Gatti, R.A., 1985. Lymphocyte subpopulations in ataxia-telangiectasia. Kroc Found. Ser. 19, 309–314.
Webb, C.J., Wu, Y., Zakian, V.A., 2013. DNA repair at telomeres: keeping the ends intact. Cold Spring Harb. Perspect. Biol. 5.
Weiss, B., Krauthammer, A., Soudack, M., Lahad, A., Sarouk, I., Somech, R., Heimer, G., Ben-Zeev, B., Nissenkorn, A., 2015. Liver disease In pediatric patients with ataxia telangiectasia: a novel report. J. Pediatr. Gastroenterol. Nutr. 62, 550–555.
Weizman, N., Shiloh, Y., Barzilai, A., 2003. Contribution of the Atm protein to maintaining cellular homeostasis evidenced by continuous activation of the AP-1 pathway in Atm-deficient brains. J. Biol. Chem. 278, 6741–6747.
Wong, K.K., Maser, R.S., Bachoo, R.M., Menon, J., Carrasco, D.R., Gu, Y., Alt, F.W., DePinho, R.A., 2003. Telomere dysfunction and Atm deficiency compromises organ homeostasis and accelerates ageing. Nature 421, 643–648.
Wood, L.D., Halvorsen, T.L., Dhar, S., Baur, J.A., Pandita, R.K., Wright, W.E., Hande, M.P., Calaf, G., Hei, T.K., Levine, F., Shay, J.W., Wang, J.J., Pandita, T.K., 2001. Characterization of ataxia telangiectasia fibroblasts with extended life-span through telomerase expression. Oncogene 20, 278–288.
Worgul, B.V., Smilenov, L., Brenner, D.J., Junk, A., Zhou, W., Hall, E.J., 2002. Atm heterozygous mice are more sensitive to radiation-induced cataracts than are their wild-type counterparts. Proc. Natl. Acad. Sci. U. S. A. 99, 9836–9839.
Worgul, B.V., Smilenov, L., Brenner, D.J., Vazquez, M., Hall, E.J., 2005. Mice heterozygous for the ATM gene are more sensitive to both X-ray and heavy ion exposure than are wildtypes. Adv. Space Res. 35, 254–259.
Worth, P.F., Srinivasan, V., Smith, A., Last, J.I., Wootton, L.L., Biggs, P.M., Davies, N.P., Carney, E.F., Byrd, P.J., Taylor, A.M., 2013. Very mild presentation in adult with classical cellular phenotype of ataxia telangiectasia. Mov. Disord. 28, 524–528.
Wu, D., Yang, H., Xiang, W., Zhou, L., Shi, M., Julies, G., Laplante, J.M., Ballard, B.R., Guo, Z., 2005. Heterozygous mutation of ataxia-telangiectasia mutated gene aggravates hypercholesterolemia in apoE-deficient mice. J. Lipid Res. 46, 1380–1387.
Xi, H., Li, C., Ren, F., Zhang, H., Zhang, L., 2013. Telomere, aging and age-related diseases. Aging Clin. Exp. Res. 25, 139–146.
Xia, S.J., Shammas, M.A., Shmookler Reis, R.J., 1996. Reduced telomere length in ataxia-telangiectasia fibroblasts. Mutat. Res. 364, 1–11.
Yamashita, A., Kashima, I., Ohno, S., 2005. The role of SMG-1 in nonsense-mediated mRNA decay. Biochim. Biophys. Acta 1754, 305–315.
Yang, D.Q., Kastan, M.B., 2000. Participation of ATM in insulin signalling through phosphorylation of eIF-4E-binding protein 1. Nat. Cell Biol. 2, 893–898.
Yi, M., Rosin, M.P., Anderson, C.K., 1990. Response of fibroblast cultures from ataxia-telangiectasia patients to oxidative stress. Cancer Lett. 54, 43–50.
Zhang, N., Song, Q., Lu, H., Lavin, M.F., 1996. Induction of p53 and increased sensitivity to cisplatin in ataxia-telangiectasia cells. Oncogene 13, 655–659.
Zhang, J., Kim, J., Alexander, A., Cai, S., Tripathi, D.N., Dere, R., Tee, A.R., Tait-Mulder, J., Di Nardo, A., Han, J.M., Kwiatkowski, E., Dunlop, E.A., Dodd, K.M., Folkerth, R.D., Faust, P.L., Kastan, M.B., Sahin, M., Walker, C.L., 2013. A tuberous sclerosis complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS. Nat. Cell Biol. 15, 1186–1196.
Zhang, J., Tripathi, D.N., Jing, J., Alexander, A., Kim, J., Powell, R.T., Dere, R., Tait-Mulder, J., Lee, J.H., Paull, T.T., Pandita, R.K., Charaka, V.K., Pandita, T.K., Kastan, M.B., Walker, C.L., 2015. ATM functions at the peroxisome to induce pexophagy in response to ROS. Nat. Cell Biol. 17, 1259–1269.
Zhu, Y., Armstrong, J.L., Tchkonia, T., Kirkland, J.L., 2014. Cellular senescence and the senescent secretory phenotype in age-related chronic diseases. Curr. Opin. Clin. Nutr. Metab. Care 17, 324–328.
Zhu, Y., Tchkonia, T., Pirtskhalava, T., Gower, A., Ding, H., Giorgadze, N., Palmer, A.K., Ikeno, Y., Borden, G., Lenburg, M., O'Hara, S.P., LaRusso, N.F., Miller, J.D., Roos, C.M., Verzosa, G.C., LeBrasseur, N.K., Wren, J.D., Farr, J.N., Khosla, S., Stout, M.B., McGowan, S.J., Fuhrmann-Stroissnigg, H., Gurkar, A., Zhao, J., Colangelo, D., Dorronsoro, A., Ling, Y.Y., Barghouthy, A.S., Navarro, D.C., Sano, T., Robbins, P.D., Niedernhofer, L.J., Kirkland, J.L., 2015. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell 14, 644–658.
Ziv, Y., Bar-Shira, A., Pecker, I., Russell, P., Jorgensen, T.J., Tsarfati, I., Shiloh, Y., 1997. Recombinant ATM protein complements the cellular A-T phenotype. Oncogene 15, 159–167.
Ziv, S., Brenner, O., Amariglio, N., Smorodinsky, N.I., Galron, R., Carrion, D.V., Zhang, W., Sharma, G.G., Pandita, R.K., Agarwal, M., Elkon, R., Katzin, N., Bar-Am, I., Pandita, T.K., Kucherlapati, R., Rechavi, G., Shiloh, Y., Barzilai, A., 2005. Impaired genomic stability and increased oxidative stress exacerbate different features of ataxia-telangiectasia. Hum. Mol. Genet. 14, 2929–2943.
Zolner, A.E., Abdou, I., Ye, R., Mani, R.S., Fanta, M., Yu, Y., Douglas, P., Tahbaz, N., Fang, S., Dobbs, T., Wang, C., Morrice, N., Hendzel, M.J., Weinfeld, M., Lees-Miller, S.P., 2011. Phosphorylation of polynucleotide kinase/phosphatase by DNA-dependent protein kinase and ataxia-telangiectasia mutated regulates its association with sites of DNA damage. Nucleic Acids Res. 39, 9224–9237.