Increased Oxidative Stress in Ataxia Telangiectasia Evidenced by Alterations in Redox State of Brains from Atm-deficient Mice

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Abstract

Ataxia-telangiectasia (A-T) is a genetic disorder caused by mutational inactivation of the ATM gene. A-T patients display a pleiotropic phenotype and suffer primarily from progressive ataxia caused by degeneration of cerebellar Purkinje and granule neurons. Disruption of the mouse Atm locus creates a murine model of A-T that exhibits most of the clinical features of the human disease. We previously hypothesized that some aspects of A-T, such as the preferential loss of certain neurons, could result from a continuous state of increased oxidative stress (G. Rotman and Y. Shiloh, Cancer Surv., 29: 285–304, 1997; G. Rotman and Y. Shiloh, BioEssays, 19: 911–917, 1997). The present work tests this hypothesis by analyzing markers of redox state in brains of Atm-deficient mice. We found alterations in the levels of thiol-containing compounds in Atm (−/−) brains, as well as significant changes in the activities of thioredoxin, catalase, and manganese superoxide dismutase in Atm (−/−) cerebella. These changes are indicative of increased levels of reactive oxygen species, which are seen primarily in the cerebellum of Atm-deficient mice. Our findings support the hypothesis that the absence of functional ATM results in oxidative stress, which may be an important cause of the degeneration of cerebellar neurons in A-T.

Introduction

A-T is an autosomal recessive disorder characterized by progressive cerebellar ataxia, immunodeficiency, premature aging, gonadal dysgenesis, extreme radiosensitivity, and high incidence of lymphoreticular malignancies (reviewed in Ref. 1). Functional inactivation of the ATM gene product accounts for this compound phenotype (2, 3). ATM, the product of the ATM gene, is a member of a family of large proteins found in various organisms that share a COOH-terminal PI3 kinase-like domain. ATM has serine/threonine protein kinase activity and mediates the activation of multiple signal transduction pathways (reviewed in Refs. 4 and 5). Atm-null mice, which were created by disrupting the Atm locus (6–8), recapitulate the human A-T phenotype and display growth retardation, mild neurological dysfunction, male and female infertility, extreme predisposition to thymic lymphomas, and acute sensitivity to ionizing radiation. The availability of these mice provides a model on which to explore the nature of this disease.

Cells derived from A-T patients and Atm-deficient mice exhibit genomic instability and hypersensitivity to ionizing radiation and other treatments that generate ROS. Several lines of evidence suggest that these characteristics result from abnormal processing of DNA double-strand breaks and aberrant activation of multiple cellular responses to genotoxic damage (reviewed in Refs. 5, 9, and 10). Treatment of cells with ionizing radiation generates increased production of ROS, including hydroxyl radicals, superoxide anion, and hydrogen peroxide. ROS are also produced during normal metabolic activities catalyzed by mitochondrial electron transport and other redox reactions that take place in microsomes and the inner plasma membrane surface (reviewed in Refs. 11–13). At nontoxic concentrations, ROS may play a role in signal transduction (13–15), but at higher levels they can inflict oxidative damage to cellular components, resulting in lipid peroxidation, protein and DNA oxidation, and disruption of cellular thiol status (reviewed in Refs. 11 and 16).

Cells have evolved a wide array of protection mechanisms against ROS, including small reducing molecules, antioxidant enzymes, and damage-repair systems (reviewed in Refs. 11, 12, 16, and 17). One of the reducing molecules is glutathione, which appears in the cells in both its oxidized (GSSG) and reduced (GSH) forms, and can function by itself or in association with enzymatic activities. Several enzymes are responsible for detoxifying specific ROS: SOD, which converts superoxide radicals into H$_2$O$_2$ and O$_2$; catalase and glutathione peroxidase, which are scavengers of hydrogen peroxide; and glutathione-S-transferases, which are a large family of multifunctional dimeric enzymes that conjugate GSH to electrophilic centers in hydrophobic organic compounds, including lipid peroxides (reviewed in Ref. 18). There are also auxiliary enzymes: glutathione reductase which generates GSH from GSSG using NADPH, and glucose-6-phosphate dehydrogenase (G6PD), which recycles NADPH using energy derived from cellular metabolism. In addition to ROS-detoxifying enzymes, there are damage repair enzymes such as thioredoxin, a small ubiquitous protein that has a variety of activities as hydrogen donor and acts as a major protein oxidoreductase (reviewed in Refs. 19 and 20).

Overwhelming the cellular antioxidative capacity by increased ROS results in oxidative stress (12). We recently hypothesized that the absence of a functional ATM could result in a continuous state of oxidative stress, leading to the demise of particularly sensitive cells such as neurons (21, 22). In the present work, we explored the prevalence of oxidative stress associated with ATM deficiency in the CNS. Atm-null mice were used to study cellular markers of excessive production of ROS, including activities of antioxidant enzymes, tissue concentrations of GSH and its precursor cysteine, protein oxidation, and lipid peroxidation. Significant changes were found in the levels of glutathione and cysteine, and in the activities of thioredoxin, catalase, and Mn-SOD activities that take place almost exclusively in the cerebella of Atm (−/−) animals. These results are indicative of increased oxidative stress in Atm-deficient mice that is manifested primarily in the area of the CNS most affected in A-T patients, the cerebellum.

Materials and Methods

Mice. Atm (+/−) mice (6) were a generous gift from Dr. Wynshaw-Boris (NIH, Bethesda, MD). Offspring of these mice were genotyped by PCR-based assays using mouse-tail DNA, prepared with GeneReleaser reagent (BioVentures Co, Murfreesboro, TN).
**Tissue Collection and Preparation of Tissue Extracts.** After anesthetizing the mice by CO<sub>2</sub>-induced asphyxiation, tissues were removed, washed with cold PBS, and stored at −70°C after rapid freezing in liquid nitrogen. Prior to assays, samples were thawed and homogenized in 50 mM phosphate buffer (pH 7.2) 0.1% Triton X-100, in the presence of a protease inhibitor cocktail (Boehringer, Mannheim, Germany). The extracts were sonicated twice for 15 s and centrifuged for 1 h at 89,000 × g, after which the supernatants were collected and used for the enzyme assays. Protein concentrations were determined by the Bradford method (Ref. 23; Bio-Rad, Hercules, CA).

**Determination of Low M<sub>1</sub>, Thiol Groups.** Thiol-containing compounds were determined using high-performance liquid chromatography with a reverse-phase C18 column. Tissue extracts were reacted with monobromobimane. The data were analyzed using Millennium software.

**Measurement of Enzyme Activities: Antioxidant and Accessory Enzymes.** Assays were performed with tissue extracts within 48 h of their preparation, during which they were stored at 4°C. Catalase activity was determined by polarography by following O<sub>2</sub> production with a Clark-type oxygen electrode (Hamtech, Norfolk, UK), in a reaction mixture containing 100 mM potassium phosphate (pH 7.2) and 20 mM H<sub>2</sub>O<sub>2</sub>. The reaction was run at 30°C for 1 min, but only the initial linear rate was included in the activity calculations. One unit of enzyme activity was defined as that which resulted in the decomposition of 1 μmol H<sub>2</sub>O<sub>2</sub>/min at an initial concentration of 20 μM H<sub>2</sub>O<sub>2</sub>. The levels of blood catalase activity were measured and normalized to hemoglobin concentrations. Hemoglobin concentration was measured in the samples and found to be very low.

SOD activity was measured by spectrophotometry by following the inhibition of cytochrome reduction using xanthine-xanthine oxidase as a source of superoxide (24). The assay mixture for total SOD activity contained, in a final concentration of 1 μM xanthine, 5–20 μM xanthine oxidase, and varying concentrations of tissue extracts. The reduction of the acetylated cytochrome c was determined from an initial absorbance change at 550 nm, started by the addition of xanthine oxidase. The activity of Mn-SOD was determined by running the reaction in the presence of 5 mM cyanide, which is a potent inhibitor of Cu/Zn-SOD. The activity of Cu/Zn-SOD was calculated by subtracting Mn-SOD activity from the total SOD activity.

Glutathione peroxidase (Gpx) activity was determined using spectrophotometry by the method of Flohe and Gunzler (25). Glutathione transferase (Gst) activity was assayed using a spectrophotometric method described previously (26). Glutathione reductase (Gxr) activity was assessed using a spectrophotometric method described previously (27).

Glucose-6-phosphate dehydrogenase (G6PD) activity was assayed using a spectrophotometric method described previously (28).

**Measurement of Thioredoxin Activity.** Thioredoxin activity was assayed using the micro-method of insulin reduction, as previously described (29). The assay mixture containing 100 mM Tris-HCl (pH 7.6), 150 mM NaCl, and a catalytic amount of protease inhibitors (Boehringer, Mannheim, Germany) and centrifuged (for 2 min at 15,000 × g). Cell lysates were kept at −20°C until assay. The reaction mixture containing the following in a final volume of 39 μl: 0.26 μl Tris-HCl (pH 7.6), 0.01 μl EDTA, 2 μM NADPH, and 1 μM insulin. Tissue extracts and thioredoxin reductase (TR; purified from rat liver) were added, and the mixture was incubated at 37°C for 20 min. The reaction was stopped by the addition of 162 μl of 0.2 mg/ml DTNB/6 μg guainidine hydrochloride in 0.2 M Tris-HCl (pH 8), and the absorbance at 412 nm was recorded. A blank reaction consisting only of reaction mixture served as a negative control. Another control was obtained by determining the level of SH groups in the tissue extract in the absence of thioredoxin that species; for this purpose, the absorbance of the tissue extract in the presence of DTNB/guainidine hydrochloride was measured. Thioredoxin activity was the total sample absorbance minus the absorbance of the blank and the absorbances of the SH groups.

**Determination of Protein Carbons.** Because oxidative modifications of proteins are accompanied by the generation of protein carbonyls that react with 2,4-DNPH (2,4-dinitrophenylhydrazine, Sigma, D-2630) to form protein hydrazine derivatives, this property was used to look for evidence of oxidative damage to proteins in Atm (−/−) brains. Aliquots of cerebellar and cerebral homogenates were derivatized using 2,4-DNPH and examined by Western blot analysis with anti-dinitrophenyl antibodies (DAKO, Glostrup, Denmark), as described previously (30).

**Determination of Lipid Peroxidation.** Lipid peroxides were assessed with the BIOXYTECH LPO 586 kit (OXIS International Inc., Portland, OR), which measures malonaldehyde (MDA) and 4-hydroxyalkenals that result from peroxidation of polyunsaturated fatty acids.

**Statistical Analysis.** Results were analyzed using the Mann-Whitney U test for nonparametric data and the two-tailed Student t test. Data were expressed as mean ± SE, and Ps ≤ 0.05 were considered significant.

## RESULTS

**Thiol-containing Compounds in Cerebella and Cerebra of Atm (+/+) and (−/−) Mice.** The levels of GSH and cysteine in the cerebella of Atm (+/+) mice increased (43% and 81%, respectively) between the ages of 1 and 2 months, and remained unchanged in Atm (−/−) mice (Fig. 1, A and C). The levels of cysteine in Atm (−/−) cerebella were significantly lower (41.1%) at 2 months than in Atm (+/+) cerebella (P < 0.0252; Fig. 1A). The cysteine levels in the cerebrum of both Atm (+/+) and Atm (−/−) mice declined with age (Fig. 1B) but were lower in Atm (−/−) cerebra (38%, P < 0.0215; at 2 months of age; Fig. 1B). On the other hand, cerebral levels of GSH in 1-month-old Atm (−/−) mice were significantly higher (33%) than in their Atm (+/+) littermates (P < 0.0286; Fig. 1D). According to our results, age-dependent changes occur in the profile of thiol-containing compounds in the cerebellum of Atm (+/+) but not Atm (−/−) mice, resulting in considerably lower levels of these compounds in the cerebella of Atm-deficient mice. These data, together with significant differences observed between cerebra of Atm (−/−) and Atm (+/+) mice, indicate age-dependent generation of oxidative stress in the absence of Atm.

**Increased Activity of Thioredoxin in Atm (−/−) Cerebella.** Thioredoxin is a general reductase that catalyzes NADPH-dependent reduction of exposed S-S disulfide bond bridges in a variety of proteins. Its levels and activity are increased in cells exposed to oxidative stress (31–33).3 To study whether the absence of the Atm protein affects the redox-state homeostasis, the activity of thioredoxin extracted from Atm (−/−) and (+/+) brains was measured. There was a 2.27-fold elevation (P < 0.0007) in thioredoxin activity in the cerebellum and a 1.53-fold increase (P < 0.19) in the cerebrum of Atm (−/−) mice compared with Atm (+/+) littermates (Fig. 2). The elevated activity of thioredoxin may indicate an adaptation to increased oxidative stress in Atm (−/−) brains.

**Decreased Catalase Activity in Atm (−/−) Cerebella.** The activity of catalase, a scavenger of H<sub>2</sub>O<sub>2</sub>, in the normal cerebellum fluctuated with age, and was generally lower in Atm (−/−) mice than in their Atm (+/+) littermates (Fig. 3A). There was a significant reduction in cerebellar catalase activity of Atm (−/−) mice, which reached significant levels at the age of 4 months (45%, P < 0.0127; Fig. 3A). On the other hand, no differences in catalase activity were detected between cerebra (Fig. 3B) and livers (data not shown) of Atm (−/−) and (+/+) littermates. Western blot analysis of the levels of catalase protein in cerebella and cerebrum did not show significant differences between Atm (−/−) and (+/+) mice (data not shown). These results demonstrate a reduction in the activity of catalase in

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3 Unpublished observations.
Fig. 1. Determination of thiol groups in cerebellum and cerebrum of ATM (−/−) and (+/+). Mean levels of cysteine (A and B) and glutathione (C and D) extracted from cerebella and cerebra of 1- and 2-month-old ATM (+/+)(E) and ATM (−/−)(F) mice. n = 12 ATM (+/+)(E) mice and n = 7 ATM (−/−)(F) mice in each experiment. Significance: *<i>P</i> 0.05; **<i>P</i> 0.001. Error bars ± SE. Statistical analyses were performed with two-tailed Student’s t test.

Fig. 2. Thioredoxin activity in ATM-deficient mice. Mean levels of thioredoxin activity in cerebella and cerebra of 2-month-old ATM (+/+)(G) and ATM (−/−)(H) mice. n = three animals of each genotype. Significance: ***<i>P</i> 0.001. Error bars ± SD. Statistical analyses were performed with two-tailed Student’s t test.

Atm (−/−) mice, which is specific to the cerebellum and may result in higher intracellular levels of H₂O₂.

**Increased SOD Activity in Atm (−/−) Cerebella.** By 4 months of age, there was a significant increase in the total SOD (Cu/Zn-SOD and Mn-SOD) activity in the cerebella of Atm (−/−) mice (97%, <i>P</i> < 0.025), compared with (+/+)(E) mice; Fig. 4A). In contrast, a smaller and insignificant increase (37%, <i>P</i> < 0.064) in total SOD activity was observed in the cerebella of Atm (−/−) compared with Atm (+/+)(E) mice (Fig. 4A). Although a significant increase in Mn-SOD activity (2.18-fold, <i>P</i> < 0.037) was observed in Atm (−/−) cerebella compared with Atm (+/+)(E) mice, the increase in Cu/Zn-SOD activity did not reach statistical significance (2-fold, <i>P</i> < 0.109). No such increase in Mn-SOD and Cu/Zn-SOD was observed in the cerebella of Atm (−/−) mice (data not shown). These results show that the increase in the activity of Mn-SOD in Atm (−/−) mouse is not associated with increased expression.

**The Activity of Other Antioxidant and Auxiliary Enzymes in Atm (−/−) Brains.** There were no significant differences in the activities of glutathione peroxidase, glutathione reductase, glutathione transferase, and glucose-6-phosphate dehydrogenase between Atm (−/−) and (+/+)(E) cerebella and cerebra of 4-month-old mice (data not shown).

**Protein Oxidation and Lipid Peroxidation in Atm-deficient Mice.** Protein oxidation patterns in Atm (−/−) cerebella and cerebra were indistinguishable from the pattern of wild-type animals (data not shown). When the degree of oxidative damage to lipids was determined by quantifying levels of malonaldehyde, the peroxidation product of polyunsaturated fatty acids, no significant differences were detected between the cerebella and cerebra of Atm (−/−) and (+/+)(E) cerebella and cerebra of 4-month-old mice (data not shown). Thus, using these methods, we could not find evidence of increased oxidative damage to proteins or lipids in the absence of Atm.

**DISCUSSION**

Our previous work suggesting that oxidative stress might play a role in the clinical and cellular manifestations of A-T (21, 22) was based primarily on indirect evidence. The present work reports data which, together with a recent report (34), indicate a prevalence of oxidative stress in certain tissues of Atm-deficient mice. Several of our findings support this notion: (a) alterations in levels of thiol-containing compounds, GSH and cysteine, point to redox changes in the cerebella and cerebra of Atm (−/−) mice. Elevated GSH might reflect a compensatory mechanism to deal with overproduction of ROS, in which case the decrease in its precursor, cysteine, would be the result of its use for increased glutathione biosynthesis; (b) in-
creased activity of thioredoxin in the cerebella Atm (−/−) mice points to changes in the redox state; and (c) changes in activities of antioxidant enzymes in Atm (−/−) cerebella, including a significant increase in Mn-SOD activity and a significant decrease in catalase activity, indicate elevated intracellular levels of ROS.

Barlow et al. (34) also provided evidence of oxidative stress in Atm-deficient mice, bringing data that showed a dramatic increase in heme oxygenase activity in the cerebellum of Atm (−/−) mice that was strongly suggestive of increased oxidative stress. Our findings of alterations in thiol levels and in the activities of thioredoxin, Mn-SOD, and catalase in Atm-deficient cerebella further support the notion that the absence of Atm leads to increased steady-state levels of ROS. Further support for this notion comes from a recent study that showed that Atm-deficient mice, injected with salicylate, generated significantly higher levels of 2,3-dihydrobenzoic acid in the basal ganglia (3.5-fold increase) and in the cerebellum (7.5-fold increase) compared with their Atm (+/+ ) littermates, which suggests that higher levels of hydroxyl radicals are generated in these tissues.6 Furthermore, use of the oxidized fluorescent dye dihydroethidium revealed that Atm-deficient cerebella had a higher number of fluorescently labeled Purkinje cells, which contained higher levels of free radicals. It is important to emphasize that the levels of different ROS (O2·−, OH− and H2O2) are interdependent.

Our findings are also in agreement with previous reports on A-T cells, in which a slight elevation in SOD activity was detected in an A-T lymphoblastoid cell line (35), lower levels of catalase activity were found in A-T fibroblasts (36, 37), and lower antioxidative capacity was reported in the plasma of A-T patients (38). Furthermore, it has been shown that chicken Atm (−/−) DT40 cells are more susceptible to apoptotic death induced by oxidative stress and that these cells exhibit a decreased capacity to detoxify ROS (39).

Despite the growing evidence of significant alterations in the redox homeostasis of Atm-deficient cells, particularly in specific tissues such as cerebellum, data showing oxidative damage to proteins and lipids of Atm (−/−) tissues are sparse. Barlow et al. (34) detected increased nitrotyrosine levels in extracts of the brain, but not of the liver, of Atm (−/−) mice, which indicated NO-mediated oxidative damage of proteins. However, in agreement with our results, there were no significant differences in carbonyl levels in proteins, pointing to a specific type of oxidative damage mediated by NO. This free radical acts as a neurotransmitter and is produced in large amounts in granule and basket cells of the cerebellum. Purkinje cells do not synthesize NO but receive it through synapses from the surrounding neurons (reviewed in Ref. 40). NO reacts with the superoxide anion at very high affinity, resulting in the formation of the peroxynitrite anion, a powerful oxidant. Although a critical balance between NO and superoxide usually exists in cells, a rise in the concentration of the......
latter increases the prevalence of oxidation reactions of NO, leading to its toxicity (reviewed in Refs. 41 and 42). Thus, a rise in the intracellular levels of ROS in Atm-deficient cerebella could result in increased NO-mediated damage, a possibility supported by the higher levels of nitrotyrosine detected in proteins of Atm-deficient neuronal tissues (34). Analysis of lipid peroxidation by quantification of F2-isoprostanes showed elevated levels in testes of Atm-deficient mice and only a slight, but not statistically significant, increase in thymus and brain (34). Our measurements of malonaldehyde levels also did not show significant oxidative changes in lipids of Atm (+/−) brain tissues. It is possible that Atm-deficient cells do succumb progressively to a mild but continuous state of oxidative stress, but most of the oxidative damage inflicted to their macromolecules is below detection.

Elevated ROS levels and changes in the activities of ROS detoxifying enzymes have also been reported in cells derived from patients with other genetic disorders, including XP, Bloom’s syndrome, Fanconi anemia, and Cockayne syndrome (43–45). These patients also display impaired repair of DNA damage, genomic instability, and premature aging. It is possible that oxidative stress is the common denominator in these diseases, although it remains unclear whether elevated ROS represent the primary factor or are toxic products secondary to tissue damage. Like Atm-deficient cells, XP and Bloom’s syndrome cells have significantly lower catalase activity (36). A clear correlation was recently shown between reduced catalase activity and a decrease in intracellular NADPH levels in XP (46). These researchers (46) proposed that low catalase activity in these diseases may be a consequence of permanent cellular stress attributable to accumulated DNA lesions that produce a drop in intracellular levels of NADPH, a cofactor of this enzyme.

It is not clear how the absence of ATM results in changes in the cellular redox state. ATM is a large multifunctional protein that is present primarily in the nucleus of dividing cells, in which it is involved in sensing DNA double-strand breaks and activating numerous damage-induced pathways. A variable fraction of ATM is localized in the cytoplasm, in which it is generally found in conjunction with microtubules (47–49). The ATM protein was detected in the developing cerebellum but not in the rest of the human CNS. Furthermore, ATM distribution appears to be restricted to the cytoplasm of Purkinje cells (50). A similar cytoplasmic localization of the Atm protein was observed in young mice (51). Watters et al. (37) have shown that ATM is colocalized with the peroxisomal matrix protein catalase, which suggests a role of ATM in regulating catalase activity. Taken together, these data suggest a cytoplasmic role for ATM, perhaps in controlling cellular responses to oxidative stress in cerebellar neurons. An alternative explanation for the oxidative stress observed in the absence of ATM is that the continuous presence of unrepaird damage results in the depletion of NADPH and reduced levels of catalase activity, as was proposed for XP (46).

The elevation of SOD activity, mainly Mn-SOD, in the absence of ATM could be a response to the overproduction of superoxide, because synthesis of this enzyme was shown to be induced by this oxidant. Increased SOD, combined with decreased catalase activity, would most likely lead to higher cellular levels of H2O2, one of the most stable ROS that has been shown to act as a messenger in cellular signal transduction pathways (reviewed in Ref. 15). Thus, in addition to oxidative damage to macromolecules, elevations in H2O2 concentrations could disrupt the intricate web of signaling pathways, leading to severe cellular dysfunction and ultimately to cell death.

Glutathione peroxidase activity is higher than catalase activity in neuronal cells. Thus, if neuronal cells accumulate high levels of H2O2, they will immediately cross the cell membrane to be neutralized in the glial cells, because they are uncharged molecules and behave like water molecules regarding membrane permeability. The fact that the catalase activity in cerebellar extracts in our study was not lower than glutathione peroxidase suggests that the major activity of catalase takes place in glial cells. Indeed, in astroglial cells, glutathione peroxidase and catalase are able to substitute for each other (52).

The alleged increase of ROS in Atm-deficient mice is tissue specific and occurs mainly in the cerebellum. This is one of the tissues most affected in A-T, and these findings may point to the underlying cause of the neurodegeneration.

Mounting clinical and experimental evidence heralds the involvement of oxidative stress in the pathogenesis of other neurodegenerative disorders such as amyotrophic lateral sclerosis, and Parkinson’s and Alzheimer’s diseases (reviewed in Refs. 41, 53, and 54). Interestingly, Atm-deficient mice exhibit severe degeneration of tyrosine hydroxylase-positive, dopaminergic nigro-striatal neurons (55), a phenomenon observed in Parkinson’s disease (reviewed in Ref. 56).

Oxidative stress could be a common denominator for the loss of these neurons in Atm-deficient brains and in those suffering from Parkinson’s disease.

We have demonstrated here that Atm-deficient brains, and in particular the cerebellum, are under oxidative stress. Barlow et al. (34) showed that other organs that develop pathological changes in Atm (+/−) mice, namely the testes and thymus, exhibit oxidative stress-induced damage. These findings support our hypothesis that oxidative stress may play a role in cellular degeneration in A-T and may explain some of the diverse aspects of this pleiotropic disorder, such as progressive neurodegeneration, immunodeficiency, and premature aging. If proven correct, a better control of ROS levels could offer novel therapeutic approaches to help alleviate some of the symptoms associated with A-T, foremost its neurodegeneration.

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