Ataxia Telangiectasia-mutated Protein Can Regulate p53 and Neuronal Death Independent of Chk2 in Response to DNA Damage*

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DNA damage is a key initiator of neuronal death. We have previously shown that the tumor suppressor p53, in conjunction with cyclin-dependent kinases (CDKs), regulates the mitochondrial pathway of death in neurons exposed to genotoxic agents. However, the mechanisms by which p53 is regulated is unclear. Presently, we show that p53 is phosphorylated on Ser-15 following DNA damage and this occurs independently of the CDK pathway. Instead, we show that p53 phosphorylation, stability, as well as neuronal death is regulated, in part, by the ataxia telangiectasia-mutated (ATM) protein. Previous reports have suggested that ATM regulation of p53 occurs through Chk2. However, in our present paradigms, we show that ATM functions separately from Chk2 to regulate p53 stability and neuronal death. Chk2 deficiency does not affect p53 stability or neuronal death induced by Topoisomerase I or II inhibition. Taken together, our results provide a model by which DNA damage can activate an ATM-dependent, Chk2-independent pathway of p53-mediated neuronal death.

DNA damage is an important initiator of neuronal death and has been implicated in a wide variety of neuropathological conditions such as stroke (1, 2), Parkinson’s disease (3–5), and Huntington’s disease (6). In addition, direct loss and impairment of neurons caused by chemotherapeutic agents has also been described (7–9). However, the mechanisms by which DNA damage induces neuronal death are not fully characterized. p53 is a critical regulator of DNA integrity and coordinates cell cycle progression, DNA repair, and apoptosis in proliferating cells. This genome surveillance function of p53 is also required for neuronal injury induced by DNA-damaging agents (14, 15), excitotoxicity (11, 16) dopaminergic toxins (4), and ischemia (12). Although this evidence exemplifies the importance of p53 in neuronal death, the signals that link DNA damage to p53 induction and activation are not clear.

p53 function is regulated in a variety of ways, which include acetylation and phosphorylation on at least 11 described sites (17, 18). These modifications regulate stability through interactions with MDM2, transactivation, and specific targeting of individual p53-regulated genes (17, 18). In terms of the latter function, it has been proposed that modification of different sites may lead to unique and defined p53 responses related to cell death or cell cycle arrest. For example, modification on Ser-15 has been shown to activate the proapoptotic p53AIP1 gene (19). The presence of a myriad of regulatory mechanisms likely contributes to the flexibility and cell specificity of p53-mediated events.

ATM and Chk2 are two regulators of p53 activation in proliferating cells exposed to DNA damage. The ataxia telangiectasia-mutated (ATM) gene is critical for cellular responses to DNA double strand breaks (DSBs) (20, 21). Patients or mice defective in this gene display defective cell cycle arrest, hypersensitivity to DNA damage, and tumor disposition (22). Numerous reports have argued that ATM mediates activation of p53 through Chk2, the mammalian homologe to the Rad53 Saccharomyces cerevisiae checkpoint gene (23, 24). In this simplified model, Chk2 is phosphorylated by ATM on several sites (25, 26), and activated Chk2, in turn, phosphorylates p53 on Ser-20, a critical residue for p53 stability (23, 27). However, ATM has also been reported to modify p53 in several ways. This includes direct phosphorylation of p53 on Ser-15 (20, 21) and phosphorylation of MDM2 (28, 29). Although Ser-15 phosphorylation has been linked to p53 stability and/or transcriptional activation (20, 21, 30), the consequences of phosphorylation of MDM2 by ATM are unknown.

We have previously reported that cortical neurons exposed to the DNA-damaging agents such as camptothecin display increased p53 levels and a requirement for p53 in death (14, 31). However, the mechanism by which this occurs is unknown. We explored the possibility that this up-regulation occurs through the ATM/Chk2 pathway. Accordingly, we examined whether ATM or Chk2 deficiency would affect p53 stability and p53-dependent death in response to DNA damage induced by topoisomerase (topo) I or II inhibition. We observed inhibition of p53 up-regulation and delay of death with ATM deficiency with both DNA-damaging conditions. However, in contrast to established models of Chk2 action in proliferating cells, Chk2 had no effect on apoptosis or p53 stability in the present death paradigms. This indicates, for the first time, that ATM can regulate p53-mediated death of neurons independently of Chk2.

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‡ The abbreviations used are: MDM2, mouse double minute 2; ATM, ataxia telangiectasia-mutated protein; DSB, double strand break; topo, topoisomerase; DEVD-AFC, Z-Asp-Glu-Val-Asp-AFC; ALLN, N-acetyl-Leu-Leu-norleucinal; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; CDK, cyclin-dependent kinase; JNK, c-Jun N-terminal kinase.
FIG. 1. DNA damage induces both Ser-15 phosphorylation of p53 and p53 levels in embryonic cortical neurons. This induction is not affected by CDK inhibition. Embryonic cortical neuronal cultures were prepared as described under “Experimental Procedures.” Total cell extract was prepared from cultures treated with camptothecin (campto; 10 μM) and/or the CDK inhibitor flavopiridol (flavo; 1 μM) for the indicated times and subject to SDS-PAGE and Western blot analysis utilizing p53- and Ser-15 phospho-p53-specific antibodies as indicated. A, a representative Western blot analyses of the time course of p53/Ser-15-p53 induction following camptothecin treatment. Actin is provided as loading controls. B, densitometric analyses of time course of the Ser-15 p53/Ser-15 p53 signal ratio following camptothecin treatment. C, a representative Western blot analyses of the time course of p53/Ser-15-p53 induction following camptothecin and flavopiridol treatment. D, densitometric analyses of the time course of Ser-15-p53 induction following camptothecin treatment alone or camptothecin/flavopiridol co-treatment. The signals were normalized to actin and described relative to the 4-h camptothecin treatment signal. The data are presented as mean ± S.E. (n = 4).

EXPERIMENTAL PROCEDURES

Materials—Camptothecin, etoposide, and poly-o-lysine were obtained from Sigma-Aldrich Chemical Co. Flavopiridol (LS6–6276, (-)-cis-5,7-dihydroxy-2-/3-chlorophenyl)-8-[4-(3-hydroxy-1-methyl)piperidiny1]-3-benzopyran-4-one) was a gift from Dr. Peter J. Worland (NCI, National Institutes of Health). DEVD-AFC was purchased from Enzyme Systems Products (Dublin, CA). Cell culture media and TaqDNA polymerase were purchased from Invitrogen. ALLN was purchased from Calbiochem-Novabiochem Corp.

Primary Embryonic Neuronal Culture—Cortical neurons were prepared from E15 mouse embryos as described previously (32). Briefly, cortical neurons were dissociated from cortex and plated in 35-mm dishes, pre-coated with poly-o-lysine (100 μg/ml), at a density of 2–3 × 10^6 cell/well or at 300,000 cells/well for each well of a 24-well plate. Neurons were cultured in serum-free medium (F12/minimum essential medium (1:1) supplemented with 6 mg/ml n-glucose, 100 μg/ml transferrin, 25 μg/ml insulin, 20 nM progesterone, 60 μM putrescine, and 30 nM selenium). Under these conditions, the cultures typically contain more than 99% neurons (33). 48 h after initial plating, camptothecin (10 μM), ALLN (50 μM), etoposide (10 μM), and/or flavopiridol (1 μM) were added to neuronal cultures as indicated.

Cell Survival—After drug treatment (as mentioned above) and at the indicated time points, the cells were lysed in 200 μl of cell lysis buffer (0.1× phosphate-buffer saline, pH 7.4, containing 0.5% Triton X-100, 2 mM MgCl2, and 0.5% cetyltrimethylammonium bromide). This disrupts the cell membrane while the nuclei remain intact and distinguishable under phase-contrast microscopy. Nuclei that display blebbing, disruption of nuclear membrane, or phase bright bodies were excluded. Percent survival was calculated as the number of live neurons in drug-treated compared with number of neurons in untreated cultures. The data are presented as mean ± S.E.

Knockout Mice—For knockout studies, each embryo was dissected and plated individually. ATM (Jackson Laboratories) and Chk2 (C57BL/6 background)-deficient neurons were obtained from embryos derived from heterozygous pairings. In each experiment, neurons acquired from wild-type littermate embryos were used as controls. ATM and Chk2 knockout embryos were genotyped as follows: ATM was genotyped using GCTGCCATACCTTGACCTATG (oIMR640) and TCCGAAATTCAGGAATTTC (oIMR641) primers to detect the wild-type allele (147 bp) and CCTGGTTGGAGACCTACATC (oIMR013) and AGGTGAGATTGACCGAGCATC (oIMR014) primers were used to detect the targeted allele (280 bp) in one PCR reaction. PCR conditions were 94°C, 3 min (1 cycle); 94°C, 20 s; 64°C, 30 s (0.5°C/cycle); 72°C, 35 s (25 cycles); and 72°C, 2 min. Chk2 was genotyped using GTGTCGCCACCACTTACCTGG (WT1) and CCCTTGCGGCTTTCATTGT (WT2) primers to detect the untargeted allele (500 bp) and CAGAGGGTGTGGCCTACTTTTA (NEO1) and CAAAATTAAAGCGACCTCATT (NEO2) to detect the targeted allele (900 bp) in two PCR reactions. For the wild type allele, the PCR conditions were 95°C, 5 min (1 cycle); 94°C, 1 min; 55°C, 1 min; 72°C, 2 min; 94°C, 20 s; 64°C, 30 s (0.5°C/cycle); 72°C, 35 s (25 cycles); and 72°C, 2 min. The PCR products were gel extracted, cloned into pGEM-T Easy Vector (Promega), and sequenced. The PCR products were gel extracted, cloned into pGEM-T Easy Vector (Promega), and sequenced. The PCR products were gel extracted, cloned into pGEM-T Easy Vector (Promega), and sequenced. The PCR products were gel extracted, cloned into pGEM-T Easy Vector (Promega), and sequenced.
min; 72 °C, 1 min (35 cycles); and 72 °C; 1 min. For the null allele, the
PCR conditions were 95 °C, 5 min (1 cycle); 94 °C, 1 min; 60 °C, 1 min;
72 °C, 1 min (35 cycles); and 72 °C; 1 min.

Caspase Activity—Caspase activity was determined utilizing DEVD-
AFC as previously described (34).

TUNEL Labeling—TUNEL analyses was performed as previously
described (35). Quantitation was performed by scoring at least 100
cells/well for TUNEL labeling, and condensed/fragmented nuclei were
visualized by Hoechst staining. The values are expressed in relation to
the total number of Hoechst (healthy plus fragmented/condensed)-pos-
tive cells.

Western Blot Analysis—Cortical neurons were dissociated and cul-
tured as mentioned above. At the indicated time points, neurons were
harvested and lysed using SDS sample buffer (62.5 mM Tris, pH 6.8, 2%
SDS, 10% glycerol, 50 mM DTT, 0.1% bromphenol blue). Whole cell
protein extracts were heated (95 °C, 5 min), and extracts were subjected
to electrophoresis on SDS-PAGE and transferred on nitrocellulose
membranes. A Western blot analysis was performed as previously de-
scribed utilizing phospho-p53 (Ser-15) antibody (Cell Signaling Tech-
nology, Inc.; 1:1000), p53-Ab-1 antibody (Oncogene Research Products;
1:1000), p53 1C12 antibody (Cell Signaling Technology, Inc.; 1:2000),
and/or MDM2 antibody (Santa Cruz Biotechnology, SMP14; 1:000). The
protein bands were detected using the horseradish peroxidase-conju-
gated secondary antibody and ECL system and subjected to densito-
metric analysis. All blots were reprobed and normalized to B-actin
(Clone AC-74; Sigma-Aldrich Chemical Co., 1:3000).

RESULTS

p53 Induction/Stability by DNA Damage Exposure—As we
(14, 32, 36) and others (15) have previously reported, exposure
of cortical neurons to the DNA-damaging agent and topo I
inhibitor, camptothecin, results in elevated p53 levels and ap-
optotic death. p53 function is an absolute requirement in this
model, because p53-deficient neurons are robustly resistant to
death (14, 15, 33). To begin to understand the mechanism by

FIG. 3. ATM deficiency attenuates the induction of Ser-15 p53 and p53
levels induced by topoisomerase I inhibition in cortical neurons. Cortical
neurons were prepared from individual embryos of an ATM heterozygous breed-
ing as described under “Experimental Procedures.” Neuronal cultures were
treated with camptothecin (campto; 10 µm) for the indicated times, and cellular
extracts were subjected to Western blot analyses with the antibodies as indicated.
A, representative Western blot analyses probed with Ser-15 p53 and p53 antibod-
ies. Blots were stripped and reprobed for MDM2, which did not change under any
condition. Actin is provided as loading controls. Densitometric analyses of
Ser-15 p53 induction (B) and p53 induction (C) in ATM (+/+) and ATM (−/−)
neurons are provided. All data are normalized to actin and are described in ar-
bitrary units. The values are presented as mean ± S.E. of four separate embryos
(n = 4).
which p53 induction is regulated, we first examined whether p53 is phosphorylated at Ser-15, a site associated with p53 stability/activity (20, 21, 37). Utilizing a phosphoepitope-specific antibody specific to this site and Western blot analyses, we observed that Ser-15 phosphorylation accompanied p53 induction (Fig. 1, A and B). When the relative ratio of Ser-15 phosphorylation/total p53 was calculated, we observed a sharp increase in the specific activity of Ser-15 phosphorylation, which preceded p53 induction. To ensure the specific nature of the Ser-15 signal, we induced p53 by use of a proteasomal inhibitor, ALLN. With this treatment, the rapid turnover of p53 is suppressed. Accordingly, p53 can accumulate without modulatory post-translational modifications such as Ser-15 phosphorylation. In comparison to p53 induction induced by DNA damage, no Ser-15 signal was observed indicating the specific nature of the Ser-15 antibody (Fig. 2).

Our previous work indicate that at least three upstream signaling pathways are necessary for activation of the conserved mitochondrial pathway of death in response to DNA damage induced by topo I inhibition. These include 1) involvement of p53 mentioned above (14), 2) activation and requirement of cyclin dependent kinases (CDKs), which normally regulate cell cycle progression (32, 36), and 3) the c-Jun N-terminal kinases (JNKs) (38). Inhibition of either the JNK or CDK pathways, although sufficient to prevent caspase activation and death had no affect on global p53 induction (14, 38). The converse was also true; inhibition of p53 blocks death without preventing the activation of the JNKs or CDKs. This suggests that CDKs, JNKs, and p53 are regulated on separate pathways, which only converge to modulate activation of the mitochondrial pathway of death (Bax translocation, cytochrome c release, and caspase activation). However, it is possible that CDKs, directly, or indirectly, may modulate post-translational modification of p53. To ensure that this was not
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the case for Ser-15 phosphorylation, we examined whether cotreatment with the CDK inhibitor flavopiridol would alter p53 Ser-15 phosphorylation. As shown in Fig. 1, the CDK inhibitor flavopiridol would alter the case for Ser-15 phosphorylation, we examined whether ATM-deficient embryos and embryos not treated or treated with etoposide or camptothecin for 12 h.

ATM/p53 and Neuronal Death Induced by DNA Damage—One candidate for regulation of p53 is ATM, and we therefore examined whether ATM deficiency would modulate the response to topo I inhibition. As shown in Figs. 3 and 4, ATM deficiency significantly reduced both Ser-15 phosphorylation and total p53 induction when compared with wild type or heterozygous controls. However, it is important to emphasize that p53 induction was not totally abolished. MDM2 levels, on the other hand, remained unchanged. ATM also did not affect the induction of c-Jun (data not shown), which we have previously reported to occur independently of p53 in this death model (38). This indicates that the effect of ATM deficiency was not general to all transcription factors and provides further evidence that p53 and c-Jun regulatory pathways are distinct. Importantly, ATM-deficient neurons were also resistant to neuronal death induced by camptothecin. As shown in Fig. 5, ATM-deficient neurons were significantly resistant to topoisomerase I inhibition-induced death when compared with heterozygous controls (~55% survival versus 25% in controls). However, unlike p53 deficiency where protection can be sustained at 3 days (14), protection by ATM deficiency was transient. Significant protection was only observed 12 h after camptothecin treatment but not at 24 h. This is likely, because p53 levels were not completely abolished. Phase micrographs reveal degenerating processes and apoptotic soma in control camptothecin-treated cultures, whereas ATM-deficient neuronal cultures had appreciably less apoptotic bodies (Fig. 6). Consistent with the protection observed by nuclear counts, ATM-deficient neurons treated with camptothecin also showed less DEVD-AFC cleavage activity, which reflects caspase 3-like activity (Fig. 7). Heterozygous control cultures showed approximately 2.5 times the activity as observed in ATM-deficient control cultures. Finally, to confirm that apoptotic death was reduced in ATM-deficient cultures, we analyzed for death by TUNEL. As shown in Fig. 8, ATM-deficient cultures also had significantly less TUNEL-positive cells when compared with littermate controls.

To confirm our findings with topo I inhibition, we also examined p53 response and death induced by etoposide, a topo II inhibitor, which produces DSBs in a more faithful fashion. As shown in Fig. 4, ATM deficiency also attenuated p53 phosphorylation/induction as well as death in response to etoposide. In case of the latter, significant protection was observed even 48 h after etoposide treatment (Fig. 5). ATM-deficient neurons treated with etoposide displayed improved morphology (Fig. 6), attenuated TUNEL labeling (Fig. 8) when compared with etoposide-treated control cultures, as well as reduced DEVD-AFC cleavage (data not shown).

Chk2, p53, and Neuronal Survival in DNA Damage—Previous reports have indicated that Chk2 plays a critical role in p53 regulation in proliferating cells, likely through phosphorylation at Ser-20 (23, 27). The consensus appears to be that Chk2 is a prerequisite for DNA damage/DSB-induced death (24, 39) and that one of ATMs critical role in controlling p53 function is to activate Chk2 (23). From this simple model, one would predict that, because ATM functions to regulate p53 and death, Chk2 deficiency should also provide similar outcomes as ATM deficiency. However, no protection was observed in Chk2-deficient neurons treated with either etoposide or camptothecin when compared with littermate controls (Fig. 9). Consistent with this observation, total p53 levels were not significantly affected with either DNA-damaging agents in Chk2-deficient neurons (Fig. 10). In addition, no significant reduction in p53 Ser-15 phosphorylation was observed in Chk2-deficient neurons treated with camptothecin or etoposide (Fig. 10) as might be expected, because Chk2 does not phosphorylate Ser-15 (23). Unfortunately, direct phosphorylation of the Ser-20 site equivalent in mouse could not be evaluated, because the Ser-20 phosphospecific antibody does not recognize mouse p53. Taken together, this data indicates that, although ATM plays a crucial role in topo inhibitor-induced neuronal death, Chk2 inhibition alone is not sufficient for modulation of the p53-mediated death response.
**DISCUSSION**

The prevailing notion of the involvement of ATM/Chk2 pathway in p53-mediated death has been that Chk2 is an absolute requirement for DNA DSB-induced death, whereas ATM involvement depends upon cellular context (23, 24, 27, 39). Interestingly, our results reveal that ATM can regulate p53 stabilization neuronal and neuronal death induced by both topo I and II inhibition independently of Chk2. This suggests that the required ATM function can be dissociated from that of Chk2 activity and indicates a more complex relationship between ATM, Chk2, and p53 in response to DNA damage.

There are several possible explanations for a seemingly ATM-dependent, Chk2-independent p53-mediated death response. First, ATM is reported to increase p53 stability through direct phosphorylation of Ser-15 (20, 21, 40). Indeed, we have shown that p53 is phosphorylated on this residue in response to two separate models of neuronal damage and that this phosphorylation is mediated by ATM. However, it is important to note that the reported function of Ser-15 phosphorylation is not completely consistent, and several reports have suggested that Ser-15 may be more important for transactivation rather than stabilization (18, 30, 41). Therefore, additional ATM-mediated events may be important. In this regard, ATM has been reported to directly phosphorylate MDM2 (28, 29).

A second possibility is that the ability of ATM to regulate p53 may require multiple mechanisms that collectively impinge upon p53 regulation. In this scenario, ATM would lie at a signaling apex that includes, but is not limited to, Chk2 activation. Chk2 may participate in p53-mediated death responses but only in the presence of other regulatory modifications such as Ser-15 phosphorylation. Indeed, it has been shown that mutation of Ser-20 alone does not affect p53 stability or death (42).

Although we do not distinguish between these above possibilities, our results are significant, because it shows that chk2 is not an absolute requirement for ATM-mediated death. This is in contrast to previous reports indicating irradiation-induced death of the developing CNS is dependent upon both ATM and

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**FIG. 8.** The induction of TUNEL labeling induced by DNA damage is attenuated in ATM-deficient neurons. *A*, representative TUNEL (red) and Hoechst (blue) labeling in ATM-deficient and control cultures treated for 12 h as indicated. *B* and *C*, quantitation of TUNEL-positive cells (*B*) and condensed/fragmented cells (*C*). The data is presented as mean ± S.E. (*n* = 3) from three separate embryos.

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Chk2 (24, 43). The possible reasons for this are several. First, although irradiation is a more standard model of DNA DSBs, damage by other agents may cause multiple processes to be activated that can compensate for Chk2 loss. This includes activation of the ATM family member ATR and Chk2 family member, Chk1. Indeed, Chk1 has also been shown to phospho-
rylate Ser-20 in vitro (44). However, whether this occurs in neurons in vivo is unknown, because Chk1-deficient mice die at an early embryonic age (45, 46). Although ATR/chk1 pathway is thought to regulate responses to DNA single strand breaks, it is possible that it may participate in p53 stabilization in systems that are dependent upon ATM. Whether Chk1 is critical for DNA damage-induced p53 responses and neuronal death in our present models will require further experimentation with neurons obtained from conditional Chk1 mutant mice. A second explanation of the differences in the involve-
ment of ATM and Chk2 in DNA damage response may be the result of neuronal maturity or neuronal type. Indeed, previous reports have shown that the reliance on caspases for death can change with neuronal maturity even with the same death stim-
uli (35, 47).

Of note, ATM deficiency down-regulated but did not com-
pletely abolish p53 induction in our present neuronal death paradigms. Consistent with this, p53 deficiency results in dramatically more protection when compared with ATM de-
iciency. This indicates that additional factors must account for p53 stability and transactivational potential. In this regard, residual activity by the ATR/Chk1 pathway may play an im-
portant role in p53 stability. However, other mechanisms of p53 control have also been described. This includes up-regula-
tion of p19ARF, which serves to block a negative regulator of p53, mdm2 (48). In addition, p53 itself contains at least 11

**FIG. 9.** Chk2 deficiency does not attenuate death of cortical neurons evoked by topoisomerase I or II inhibition. Cortical neurons were prepared from individual embryos of an ATM heterozy-
gous breeding as described under “Experimental Procedures.” Cultures were treated with camptothecin (10 μM) or etoposide (10 μM) for the indicated times and evaluated by nuclear counts. Each data point represents combined values from four separate embryos and is pre-
sented as mean ± S.E. (n = 3).
dative environment of neurons (43, 49). If correct, ATM may modulate DNA damage/stress pathways. In humans with AT, ATM appears to be the regulation of p53. However, unlike previous models of DNA damage, ATM function does not affect p53 phosphorylation (43). As a final note, ATM is vital in neurons due to its ability to modulate DNA damage/stress pathways. In humans with AT, cerebellar degeneration is a cardinal hallmark of the disease (49). Although the mechanism of this degeneration is not well understood, it has been suggested that ATM perform a critical DNA repair/surveillance function important in the highly oxidative environment of neurons (43, 49). If correct, ATM may also participate in other neuropathological conditions, which also produce oxidative stress and DNA damage.

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