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Review

The role of p53 in neuronal cell death

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Abstract

The p53 tumor suppressor gene is a sequence-specific transcription factor that activates the expression of genes engaged in promoting growth arrest or cell death in response to genotoxic stress. A possible role for p53-related modulation of neuronal viability has been suggested by the finding that p53 expression is elevated in damaged neurons in acute models of injury such as ischemia and epilepsy and in brain tissue samples derived from patients with chronic neurodegenerative diseases. Moreover, the absence of p53 has been shown to protect neurons from a wide variety of acute toxic insults. Signal transduction pathways associated with p53-induced cell death are being unraveled and suggest that intervention may prove fruitful in maintaining neuronal viability and restoring function following cytopathic insults. *Cell Death and Differentiation* (2000) **7,** 868–879.

Keywords: caspase; Bax; excitotoxicity; neuronal cell death; apoptosis

Abbreviations: Aβ, beta-amyloid protein; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; ATM, ataxia telangiectasia gene; CNS, central nervous system; ERK, extracellular signal-regulated kinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IGF, insulin-like growth factor; JNK, c-jun N-terminal kinase; MAP kinase, mitogen-activated protein kinase; MEK, MAP kinase kinase; MPTP, 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine; NGF, nerve growth factor; NMDA, N-methyl-D-glutamate; PI3-K, phosphatidylinositol 3-kinase; PIG's, p35-inducible genes; QA, quinolinic acid; Rb, retinoblastoma gene; SOD-1, superoxide dismutase-1; TUNEL, terminal deoxynucleotidyl transferase-mediated biotin dUTP nick end-labeling

The p53 gene

The p53 tumor suppressor gene encodes a nuclear phosphoprotein that functions as a key regulator of cell cycle progression and apoptosis. p53 is also recognized as belonging to a pathway responsible for DNA damage repair, which is critical for maintaining genomic stability. Loss or inactivation of the p53 tumor suppressor gene occurs in almost half of all human tumors[1] and is considered a fundamental, predisposing event in the pathogenesis of many cancers. Patients carrying germ line mutations in p53 are at higher risk for developing a variety of tumors,[2,3] and mice deficient in p53 display precocious tumor development.[4–7]

The p53 protein is upregulated in response to a diverse array of cellular stresses, including DNA damage, hypoxia, oxidative stress, ribonucleotide depletion and oncogene activation.[8,9] p53 protein levels are largely regulated in response to injury by changes in protein degradation. Recent studies have demonstrated that p53 protein levels are regulated by the MDM2 protein through a ubiquitin-dependent, proteasome-mediated pathway.[10,11] Stress signals result in stabilization of p53 protein through inhibition of MDM2-mediated degradation. The interaction between p53 and MDM2 is governed by phosphorylation reactions[12,13] and through protein–protein interactions such as those involving the p14ARF protein.[14,15] The E2F1 transcription factor, which is involved in cell cycle progression and under certain circumstances mediates apoptosis, can also regulate p53 stabilization, in part, through transcriptional activation of ARF expression.[16] Thus, a diverse but partially overlapping series of regulatory pathways may influence p53 protein levels. These regulatory pathways have been largely defined for non-neuronal cells, and there is little information regarding the regulation of p53 activity in neurons.

In response to cellular stress, p53 induces its biological response through the transcriptional transactivation of specific target genes. These downstream effectors have been characterized with respect to p53-mediated growth arrest,[17] but the pathways associated with p53-mediated apoptosis remain obscure.[18] In addition to its transcriptional transactivating activity, p53 may promote apoptosis by repressing the expression of select genes.[19,20] This particular action of p53 is not well understood, but it does not appear to depend on the presence of p53 consensus binding sites in the promoter region of repressed genes. Moreover, p53-mediated apoptosis may also occur through transcription-independent pathways requiring direct protein–protein interactions.[21,22]

p53 expression changes in response to neuronal injury

The demonstration that p53 promotes apoptosis has important implications for the central nervous system (CNS), where cell death is observed normally during development, in response to injury, and in neurodegenerative disorders such as Alzheimer's and Huntington's disease.[23–26,] Neuronal injury, especially damage mediated by excitotoxicity, has

Table 1 Various forms of brain injury or pathology associated with p53 induction

Condition	p53 Detected as	Neurons affected	References
In vivo			
Adrenalectomy	mRNA/protein	DG	154
Alzheimer's disease	protein	Cx[b]	44,45,155
Aβ transgenic mouse	protein	Cx, Hp	46
Amyotrophic lateral sclerosis	protein	SMN	45
Angelman Syndrome	protein	Cb, Hp[c]	50
Down's Syndrome	protein	Cx, Cb	45,52
Hereditary DNA repair disorders	protein	Cb	156
Ionizing radiation	protein	Ob, Cx, Cb, Hp	34
Ischemia	mRNA/protein	Cx, St, Rt	42,43,157–159
Methamphetamine	protein	St	62
Photochemical injury	protein	Cx	160
Rb deficiency	protein	NS[a]	65
Seizures/excitotoxicity	mRNA/protein	HP, Th, Am, Cx, PCx, St	35–39,161
Traumatic brain injury	mRNA	Cx, Hp, Th	40,41,162
In vitro			
Cytosine arabinoside	protein	Sp, Cb	55,70
Dopamine	p53 phosph.	Cb	163
Glutamate	mRNA/protein	Cb	53,54
6-Hydroxydopamine	protein	PC12 cells	164
Hypoxia	protein	Cx	57
Ionizing radiation	protein	Hp	56
NGF withdrawal	protein	Sp, PC12 cells[d]	74,165

[a]Not specifically stated. Ref. [65] indicated that immunocytochemical expression of p53 was increased in the central nervous system of Rb-mutant mice. Also, the absence of p53 inhibited cell death (TUNEL positive cells) in the central nervous system of Rb-mutant mice. [b]These authors reported that immunohistochemical staining demonstrated increased p53 expression and DNA fragmentation in overlapping populations of cortical neurons, and cortical and white matter glial cells distributed in regions damaged by neurodegeneration[44] A separate study demonstrated increased p53 in glial cells only.[155] [c]p53 immunoreactivity was detected in neurons in both the mouse model of Angelman Syndrome and in postmortem samples from patients with Angelman Syndrome. [d]p53 immunoreactivity shifted from the cytoplasm to the nucleus in response to NGF-induced neuronal differentiation in PC12 cells.[165] These abbreviations indicate the brain region in which p53 was detected or the region from which cultured neurons were established. Am, Amygdala; Cb, cerebellum; Cx, cerebral cortex; DG, dentate granule neurons; Hp, hippocampus; Ob, olfactory bulb; PCx, parietal cortex; Rt, Retina; Sp, sympathetic neurons; Ss, sensory; SMN, spinal motor neurons, St, striatum; Th, thalamus

been associated with increased production of reactive oxygen species,[27–30] and accumulation of single-strand DNA breaks.[31] DNA strand breaks are capable of inducing p53 accumulation,[32,33] which has prompted investigators to begin examining p53 for a role in regulating neuronal cell death.

Alterations in p53 mRNA and protein expression have been associated with neuronal damage in a variety of *in vivo* and *in vitro* model systems (Table 1). The *in vivo* models include acute injury and neurodegenerative disease. The range of acute injuries that results in p53 activation is diverse. These include adrenalectomy, which selectively promotes cell death in dentate granule cells in the hippocampus, ionizing radiation, methamphetamine administration, photochemical injury to the cerebral cortex, seizure induction produced by administration of excitatory amino acids, ischemic injury resulting from ligation of the middle cerebral artery and traumatic brain injury produced by direct impact to the cerebral cortex. In nearly all of these studies increased levels of p53 immunostaining were demonstrated in neurons. In several cases increased expression of the p53 protein was confirmed by protein immunoblotting.[34,35]

Among the acute injury models, damage resulting from neuronal stimulation by excitatory amino acids or corresponding receptor agonists has been strongly associated with p53 accumulation. The systemic injection of kainic acid, a potent excitotoxin which produces seizures associated with a defined pattern of neuronal cell loss, induced p53 expression in neurons exhibiting morphological evidence of damage;[36,37] pretreatment with a protein synthesis inhibitor prevented both kainic acid-induced p53 expression and neuronal damage. Activation of glutamate receptors by intrastriatal infusion of either N-methyl-D-aspartate (NMDA), the NMDA receptor agonist quinolinic acid (QA) or kainic acid produced a significant elevation in p53 levels in striatal neurons.[35,38,39] These results suggest that p53 induction may be linked to apoptosis due to excitotoxicity associated with seizures and Huntington's disease.

Elevated expression of the p53 gene has also been observed following experimental traumatic brain injury. As early as 6 h post-injury, p53 mRNA is induced predominantly in neurons that are vulnerable to traumatic brain injury, such as those in the contused cortex, lateral and medial geniculate nuclei of the thalamus, and the CA3 and hilar neurons of the hippocampus.[40] Interestingly, the administration of magnesium, which has been shown to be neuroprotective in experimental models of traumatic brain injury, significantly reduced p53 mRNA expression in a select population of injured neurons.[41] Transient or permanent occlusion of the middle cerebral artery causes ischemia-induced cell death in striatal and cerebral cortical neurons, which is associated with a significant increase in the expression of p53 mRNA[42] and protein.[43] In the cortex, p53 immunoreactivity was observed specifically in cortical neurons in areas surrounding the ischemic core (penumbra) one day after occlusion. Three days following middle

cerebral artery occlusion, many neurons in the penumbra region were positively stained by terminal transferase-mediated biotinylated-UTP nick end labeling (TUNEL staining). Since TUNEL labeling assesses DNA fragmentation associated with the late stages of cell death, and this occurred three days after occlusion, it is consistent with the concept that p53 may promote neuronal cell death in response to ischemia.

p53 immunoreactivity has also been detected in brain tissue derived from animal models of human neurodegenerative disease or from patients that have been diagnosed with a neurodegenerative disorder. Patients with Alzheimer's disease[44,45] show increased p53 immunoreactivity in morphologically damaged neurons consistent with the detection of extensive p53 immunoreactivity in neurons from mice overexpressing the beta-amyloid peptide (Aβ 1–42).[46] Abnormalities in the regulation of Aβ expression and processing have been associated with the development of Alzheimer's disease and neuronal degeneration.[47–49] In this particular mouse model, nuclear p53 immunoreactivity was detected in neurons that displayed cytoplasmic expression of the Aβ peptide and were TUNEL positive. A subset of neurons displayed both nuclear and cytoplasmic localization of the p53 protein whereas some neurons displayed only cytoplasmic localization. It is not clear from this report whether neurons exclusively expressing cytoplasmic p53 were also Aβ and TUNEL positive. The relationship between cytoplasmic p53 accumulation and neuronal cell death is currently unknown. However, this represents an interesting observation in light of recent findings that mutation of the E6-AP ubiquitin ligase in a mouse model of Angelman syndrome results in increased cytoplasmic abundance of the p53 protein in hippocampal pyramidal neurons and cerebellar Purkinje neurons.[50] Animals expressing the Angelman mutation display motor dysfunction, inducible seizures and a deficiency in contextual learning. Increased p53 immunoreactivity was also observed in cerebellar Purkinje cells in the brain of a patient diagnosed with Angelman syndrome. Thus, increased levels of the p53 protein in Angelman syndrome resulting from abnormalities in the ubiquitination process may contribute to neuronal dysfunction. The brains of patients with Down's syndrome, a genetic disorder manifesting a similar pathology to Alzheimer's disease, have also been shown to express elevated levels of apoptosis effectors including the p53 protein.[45,51,52] Increased p53 immunoreactivity has been localized in both neuronal and glial cell nuclei in Down's syndrome brain,[45] suggesting that p53-mediated cell death pathways may not be restricted to neurons in certain neurodegenerative disorders. These results demonstrate that increased levels of the p53 protein are commonly associated with neuronal damage and cell death in mouse models of brain injury and neurodegeneration as well as in brain tissue samples derived from patients with neurological diseases.

The results obtained with *in vitro* models of neuronal injury are consistent with the data described above for the *in vivo* models. Excitotoxicity, which figured so prominently in the whole animal studies, is a potent inducer of p53 protein in cultured cerebellar granule neurons.[53,54] Another potent stimulus for elevating p53 expression in cultured neurons is DNA damage induced by cytosine arabinoside[54,55] or ionizing radiation.[56] Hypoxia in culture, which models the ischemia produced by middle cerebral artery occlusion, increases p53 protein expression in rat embryonic cortical neurons.[57] The upregulation of p53 is associated with neurons exhibiting morphological evidence of apoptosis and the extent of upregulation is dependent upon the duration of hypoxia. Stress induced changes in p53 expression are not limited to central nervous system neurons. For example, neuronal cell death induced by nerve growth factor withdrawal dramatically elevates p53 protein levels in cultured neonatal sympathetic neurons.[58]

These results collectively demonstrate that: (1) p53 mRNA or protein can be accumulated in multiple neuronal populations in both the peripheral and central nervous system; and (2) p53 is upregulated in response to a diverse array of cellular insults ranging from hypoxia, excitotoxicity to intracellular expression of the Aβ peptide. It is not presently known if these divergent cellular insults activate p53 by initiating damage to a common cellular component (i.e., oxidative damage to DNA). Nevertheless, these studies collectively suggest that p53 is widely involved in neuronal death in response to different forms of acute insults and neurological disorders.

The relationship between p53 expression and neuronal cell death

The relationship between p53 expression and neuronal cell death has been evaluated in numerous models of injury and disease (Table 2). p53-deficient mice or neurons derived from these mice have been used most often, but inhibitors of p53 expression or p53 function have also been used to evaluate the role of p53 in the context of neuronal injury. The absence of p53 has been shown to protect neurons *in vivo* from a wide variety of toxic insults including focal ischemia,[59] ionizing radiation,[34,60] MPTP-induced neurotoxicity,[61] methamphetamine-induced neurotoxicity[62] and adrenalectomy.[63] A role for p53 has also been demonstrated for apoptosis associated with abnormal development. Homozygous deletion of the retinoblastoma gene (Rb) results in extensive apoptosis in the peripheral and central nervous system,[64] which is accompanied by increased levels of the p53 protein.[65] Backcrossing Rb-mutant mice onto a p53 null background prevents cell death in the CNS of Rb-null embryos. p53 is also essential for developmental neuronal death in certain subpopulations of neurons.[58] The naturally occurring developmental cell death of sympathetic neurons is dramatically reduced in $p53^{-/-}$ and even $p53^{+/-}$ animals.

Cultured neurons deficient in both p53 alleles exhibit protection from many toxic insults including DNA damaging agents,[55,66–70] ionizing radiation,[66,71] glutamate,[53,54,72] hypoxia,[57,73] and NGF withdrawal.[58,74] In contrast to these results, cerebellar neurons lacking p53 die when transferred to a low potassium medium[67] and postnatal cortical and hippocampal neurons also die after staurosporine exposure in a p53-independent manner.[71]

Clearly, the absence of p53 does not protect neurons against all forms of toxic insults. Cerebellar granule neuron

Table 2 Effect of p53 deletion or inhibition on neuronal survival

Condition	Protection	Neurons affected	References
In vivo			
Adrenalectomy	yes	DG	63
Amyotrophic lateral sclerosis	no	SMN	78
Developmental cell death	yes	Sp	58
Ionizing radiation	yes	NS[b], Cb	34,60
Ischemia	yes	Cx	59
Methamphetamine	yes	St	62
Methylazoxymethanol	no	Cb	60
MPTP	yes	St	61
Rb deficiency	yes	NS[a]	65
Seizures/excitotoxicity	yes/no	Cx, Hp, St, Th	35,38,79,80
In vitro			
Bleomycin	yes	Cb	68
Camptothecin	yes	Cx, Hp	69
Cytosine arabinoside	yes	Sp, Cb	55,67,70
Glutamate	yes	Cx, Hp, Cb	53,54,72
Hypoxia	yes	Cx	57,73
Ionizing radiation	yes	Cx, Hp, Cb	66,71
Low potassium	no	Cb	66
NGF withdrawal	yes/no	Sp, Ss	58,74,166,167
Staurosporine	no	Cx	71

[a]Not specifically stated. Ref. [65] indicated that immunocytochemical expression of p53 was increased in the central nervous system of Rb-mutant mice. Also, the absence of p53 inhibited cell death (TUNEL positive cells) in the central nervous system of Rb-mutant mice. [b]Not specifically stated. Ref. [34] indicated that $p53^{-/-}$ mice were resistant to irradiation-induced cell death in the developing nervous system

death induced by methylazoxymethanol is not alleviated in p53-null mice.[60] Another example relates to the role of p53-mediated apoptosis in amyotrophic lateral sclerosis (ALS), a neurodegenerative disease characterized by degeneration and death of motor neurons in the anterior horn of the spinal cord, lower brainstem, and cerebral cortex. Transgenic mice that express the copper-zinc superoxide dismutase-1 (Cu-Zn SOD1) mutations found in familial ALS kindred show progressive paralysis as a result of motor neuron cell loss.[75–77] To assess the role of p53-mediated apoptosis in ALS, mice deficient in both p53 alleles ($p53^{-/-}$) were crossed with transgenic mice expressing the G93A mutation ($G93A^+$) to create hybrid transgenic knockout mice ($G93A^+/p53^{-/-}$). Unexpectedly, the absence of p53 in these transgenic mice had no statistically significant effect on disease onset, survival, or the extent of motor neuron degeneration and showed only a minimal effect on disease progression.[78] This study provides no convincing evidence that p53 is involved in cell death in the $G93A^+$ transgenic mouse model of familial ALS. The $G93A^+$ transgenic mouse is modeled on a familial form of ALS linked to the SOD1 gene, which represents only a fraction of familial ALS kindred that account for only 5 to 10% of all ALS cases. Thus, we cannot rule out the involvement of p53 in other forms of ALS neuropathology. Nonetheless, despite evidence that p53 plays an important role in mediating cell death after acute neuronal injury, there is no definitive evidence to support such a role for p53 in late onset neurodegenerative diseases. It would be of great interest to examine whether p53-deficiency protects neurons and maintains behavioral integrity in Aβ transgenic mice[46] and in the mouse model of Angelman syndrome.[50]

The role of p53 in excitotoxicity-induced cell death is now generally accepted, although there have been occasional exceptions. In one well-characterized model of excitotoxicity, systemic injection of kainic acid produces seizures associated with a defined pattern of neuronal cell loss and increased p53 expression in neurons exhibiting morphological evidence of damage.[36,37] Neuronal cell death did not occur when this excitotoxicity model was applied to p53 knock-out mice, demonstrating that p53 induction was causally related to declining viability.[79] These findings were challenged recently by a report[80] suggesting that the lack of damage in the p53-deficient mice was attributable to the presence of a protective gene(s) introduced from the C57BL/6 strain used in the generation of the p53 deficient mouse line.[4] Schauwecker and Steward[80] reportedly induced comparable seizures in pure C57BL/6 mice and did not see any evidence of neuronal damage in the CA3 or CA1 subregion. In addition, an independent p53-deficient mouse line (on a C57BL/6 $\times$ 129/Sv background[81] but not on the 129/SvEMS background as cited[80]) did not show protection against seizure-induced neuronal cell death as opposed to the significant protection observed in the p53-deficient mice on a 129/SvEv $\times$ C57BL/6 background.[79] The basis for the apparent discrepancy between these reports[79,80] is not entirely clear.

Although C57BL/6 mice are known to be less susceptible to kainate-induced seizures[82,83] and seizure-induced damage,[84] Morrison and collegues[79] demonstrated significant neuronal damage in the CA3 and CA1 subregions of the hippocampus in p53 wild-type mice (129/SvEv $\times$ C57BL/6 background) despite the genetic contribution from the C57BL/6 strain. Others have also reported significant induction of neuronal damage in the CA3 and CA1 subregions of the hippocampus in C57BL/6 mice in response to kainate-induced seizures.[85,86] Thus, it is not clear why Schauwecker and Steward failed to

observe damage at least to the CA3 subregion of C57BL/6 mice in contrast to these other reports. Moreover, despite the contrasting results obtained with the two different p53 knock-out mice, both mouse lines were eventually shown to possess a C57BL/6 genetic background (C57BL/6 × 129/SvEv[4] *vs* C57BL/6 × 129/Sv[87]).

It is well recognized that there is a substantial genetic variability among the 129 substrains with documented phenotypic differences.[88] The variable contribution from the C57BL/6 background in the two p53 knock-out mouse strains in combination with other variations in the genetic make-up of the mice used in these experiments make it difficult to draw firm conclusions regarding the role of the purported protective genes in kainic acid-induced neuronal damage seen with one p53 knock-out mouse strain but not the other. Because of such genetic variability, it is conceivable that the excitotoxic insult induced in the p53-deficient mouse line on the C57BL/6 × 129/Sv background[80] was of such intensity that the resulting cell death was necrotic and independent of any apoptotic signaling pathways. Clearly, there are conditions in which excitatory stimulation can promote neuronal cell death independently of p53 and other cell death mediators. Indeed, Morrison *et al*[79] did report necrotic damage in the CA3 subregion of some p53-deficient mice.

Independent results confirming a role for p53 in excitotoxic cell death comes from studies involving the direct injection of excitatory amino acids into the striatum. Intrastriatally infused kainate produces neuronal death associated with increased p53 levels. Pretreatment with a cell-permeable recombinant peptide targeted to block NF-κB nuclear translocation, inhibits the kainate-induced up-regulation of p53 and internucleosomal DNA fragmentation.[35] These findings suggest that under the appropriate circumstances p53 can promote delayed neuronal cell death observed in response to excitotoxic injury.

Additional evidence to support a role for p53 in excitotoxic cell death will require the application of p53 inhibitors[89] or antisense oligonucleotides to inhibit p53 activity and suppress p53 expression, respectively. In fact, antisense oligonucleotides can suppress p53 induction and completely inhibit kainate and glutamate-induced cell death in rat cerebellar granule neurons in culture.[53] Antisense oligonucleotide-mediated p53 suppression also prevents neuronal cell death induced by hypoxia,[57] DNA damage[70] and exposure to the HIV gp120 envelope protein.[90] The adenovirus E1B55K protein has also been used to inhibit p53 function and the resultant sympathetic neuron cell death that ensues from NGF deprivation.[58] These results demonstrate that p53 function can be modulated in neurons making it possible to directly evaluate the relationship of p53 to neuronal cell death independently of genetic variations between and within different mouse strains and gene knock-out lines.

Factors regulating p53 expression in response to neuronal injury

An emerging body of evidence underscores the critical relationship between mitochondrial function, energy balance, and free radical metabolism on the one hand and neuronal viability on the other.[91–95] Mitochondrial oxidative metabolism, nitric oxide mediated processes, phospholipid metabolism and proteolytic pathways represent potential avenues for the generation of free radicals. The generation of free radicals leads to damage of cellular components such as lipids, proteins and DNA. Accumulation of DNA strand breaks is a well known stimulus for elevating p53 protein levels and for activating p53-mediated signaling pathways.[32,33] Ionizing radiation causes DNA damage and is associated with elevated p53 protein levels in neurons.[34,56] The ataxia telangiectasia (ATM) gene, whose mutation is associated with a neurodegenerative syndrome, is required for p53 activation and neuronal cell death in response to irradiation.[34,96] Developing mice lacking the ATM gene are resistant to ionizing radiation and show a significant reduction in p53 accumulation in several brain regions following irradiation.[34] However, the extent of apoptosis in the cerebellum of irradiated ATM-deficient mice is more pronounced than that in p53-deficient mice.[96] While these studies demonstrate that the ATM gene is upstream of p53, it also suggests that there may be additional signaling pathways regulating p53-dependent processes.

The stress activated kinases, particularly the Jun N-terminal kinase (JNK) and the p38 MAP kinase are activated in response to genotoxic damage[97,98] and both have been shown to phosphorylate the p53 protein.[99–101] Direct stimulation of the JNK pathway in sympathetic neurons elevates p53 protein levels and induces neuronal cell death.[58] In contrast, nerve growth factor promotes neuronal survival by binding to and activating the TrkA receptor, which, in turn, stimulates several signaling pathways including the small GTP-binding protein p21 Ras (Ras). Ras activates several downstream effector proteins, including Raf and phosphatidylinositol 3-kinase (PI3-K). Raf binds to and activates the MAP kinase kinase 1 (MEK1) and MEK2 signaling cascade, culminating in the activation of the extracellular signal-regulated kinase (ERK). Thus, the ERK pathway, which can act in direct opposition to JNK and p38 MAP kinases,[102] has been shown to protect against p53-mediated cell death in sympathetic neurons.[55] PI3-K activates the serine/threonine kinase Akt (protein kinase B), which stimulates neuronal survival[103,104] in part, through the inactivation of BAD.[105] Phosphorylated BAD is sequestered by the 14-3-3 protein releasing $Bclx_L$ to antagonize Bax.[106] The direct activation of Ras, which sits upstream of ERK, is sufficient to suppress a p53-mediated cell death pathway in sympathetic neurons.[107] Ras may inhibit p53-mediated apoptosis by suppressing p53 and bax protein levels, and Bax activity, the latter playing a key role in developmental cell death in sympathetic neurons.[108]

NF-κB is an essential survival factor in several physiological conditions, but it is also a main mediator of the cellular response to a variety of extracellular stress stimuli resulting in apoptosis. Intrastriatal administration of the excitatory receptor agonists, quinolinic acid or kainic acid, induces NF-κB nuclear translocation and increased c-*myc* and p53 mRNA and protein expression in striatal

neurons undergoing apoptosis.[35,38] The addition of an NF-κB targeted cell-permeable recombinant peptide blocks NF-κB nuclear translocation and the elevation in c-*myc* and p53 mRNA and protein expression. These effects were associated with a significant reduction in neuronal cell death, suggesting that the transcription factor NF-κB may promote neuronal apoptosis by regulating the expression of p53. Interestingly, p53 induction has been reported to cause an activation of NF-κB that correlates with the ability of p53 to induce apoptosis.[109] Thus, once induced, p53 may ensure its continued expression by activating NF-κB.

Several other unrelated molecules modulate p53 expression. These include the cations lithium and magnesium. Lithium, which has been used to treat bipolar depressive disease, protects neurons from cell death induced by middle cerebral artery occlusion,[110] an insult that increases p53 expression.[42,43] More recently, lithium has been shown to suppress glutamate-induced increases in p53 and Bax protein levels in cultured cerebellar granule neurons.[54] Administration of magnesium is neuroprotective in experimental models of traumatic brain injury. Recent evidence suggests that the neuroprotective effects of magnesium treatment may be related, in part, to down-regulation of p53 gene expression.[41] The mechanisms underlying the suppression of p53 expression by lithium and magnesium have not been identified.

A novel and potentially physiologically relevant p53 regulatory pathway has recently been described for the human amyloid precursor protein (APP). Wild-type human APP was shown to prevent cell death in a differentiated neuronal cell line in response to elevated p53 expression induced by UV irradiation, staurosporine treatment and p53-adenovirus infection.[111] Mutant forms of APP associated with familial-early onset forms of Alzheimer's disease did not confer protection. While neither form of APP altered p53 protein levels or p53 nuclear translocation, wild-type APP, in contrast to mutant APP, suppressed p53-mediated transcriptional activation from a p53-responsive promoter. The mechanism by which APP-mediated signaling altered p53 activation was not identified. However, this result suggests that naturally occurring mutations in genes predisposing individuals to neurodegeneration could enhance neuronal vulnerability to p53-mediated cell death in response to secondary insults.

In summary, these results demonstrate that: (1) p53 expression is upregulated in neurons in response to a diverse array of cellular insults, (e.g., excitotoxicity, hypoxia, ionizing irradiation, trophic factor depletion, etc.); (2) p53 expression is regulated by discrete signal transduction pathways; and (3) knowledge of these signaling pathways can be used to manipulate p53 expression in order to suppress p53-mediated cell death in neurons.

Mechanism of p53-mediated cell death in neurons

p53 promotes apoptosis by modulating the expression of select target genes. The p53 protein can function as a site-specific transactivator or a repressor of transcription.[18,112–115] Numerous pro-apoptotic genes are susceptible to regulation by p53 including Bax,[116] IGF-binding protein-3,[117] Fas,[118,119] the p53-inducible genes (PIG's)[120] and *reaper*.[121] p53 may also induce apoptosis through transcriptional repression although the mechanism for repression is not understood. Genes downregulated by p53 include bcl-2,[19] the IGF-I receptor,[122] the microtubule associated protein MAP4[123] and presenilin-1.[20] An important finding has recently suggested that p53 may promote cell death by altering the expression of enzymes that regulate the redox state of cells.[120] Therefore, one intriguing possibility is that p53-induced changes in cell viability may stem, in part, from alterations in free radical metabolism and declining mitochondrial function.[124] Disruption of the mitochondrial membrane potential and increased production of reactive oxygen species have been defined as early events in the process of neuronal apoptosis.[93,125–128]

The mechanism by which p53 specifies the neuronal response to injury is poorly understood. However, the few studies published to date utilizing neurons are in agreement with the idea that Bcl-2 family member, Bax, is essential for p53-mediated cell death in neurons. Bax-deficient neurons are protected from cell death induced by DNA damaging agents[69,96] and adenovirus-mediated p53 over-expression.[69,129] One possibility is that p53-induced changes in neuronal viability stem from declining mitochondrial function initiated by alterations in the activity of Bax. This hypothesis is consistent with the demonstration that mitochondrial dysfunction, detected as the loss of mitochondrial membrane potential and increased production of reactive oxygen species, plays an obligate role in certain forms of neuronal damage.[27–30] A relationship between Bax and alterations in mitochondrial function is substantiated by the recent demonstration that cell damage promotes Bax translocation from the cytosol to the mitochondria in COS cells[130–132] and in neurons.[133,134] Bax activation has been associated with a reduction in mitochondrial membrane potential, mitochondrial release of cytochrome c and activation of caspases.[135–139] This suggests that caspases may also be a component of the p53-induced cell death pathway sitting downstream of Bax activation.

The relationship between p53 and caspase activation has recently been examined in neurons. Recent studies indeed demonstrated that p53 is required for caspase activation in response to genotoxic stress.[69,96,129,140] These findings suggest that some forms of neuronal injury invoke a common pathway involving signal transduction through p53, Bax, mitochondrial dysfunction, cytochrome c release and caspase activation. However, other forms of injury have been shown to induce neuronal cell death by stimulating Bax translocation and caspase activation independently of p53.[141] These results demonstrate that different cellular stresses can elicit cell death by activating distinct signaling pathways culminating in Bax and caspase activation.

Caspase activation can thus be regulated by both p53-dependent and p53-independent pathways, depending upon the nature of the injury stimulus. When activated in response to a p53-dependent pathway the contribution of caspases to cell death is controversial. Caspase-3

activation is required for p53-dependent cell death in cerebellar granule neurons in response to ionizing radiation[96] consistent with results obtained in non-neuronal cells.[139,142–144] However, specific peptide inhibitors of caspases (zVAD-fmk, zDEVD-fmk and BAF) did not protect hippocampal and cortical neurons from p53-dependent cell death induced by radiation,[71] glutamate[72] or camptothecin-treatment[140] when the neuronal cultures were established from postnatal animals as opposed to embryos. In addition, adenovirus-mediated overexpression of p53 promoted neuronal cell death but did not induce caspase activity in postnatal cortical neurons.[140] Moreover, adenovirus-mediated p53 gene delivery to caspase-3 deficient postnatal cerebellar granule neurons demonstrated a delay but not complete protection from cell death.[129] These results are consistent with reports supporting the existence of caspase-independent mechanisms of programmed cell death in other cell types[135,145–147] and suggest that the requirement for caspase activity depends on the developmental status of neurons.

Clearly, additional studies are required to elucidate the downstream effectors mediating neuronal cell death in response to p53 activation. The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene has been identified as a p53-inducible gene in cultured cerebellar granule

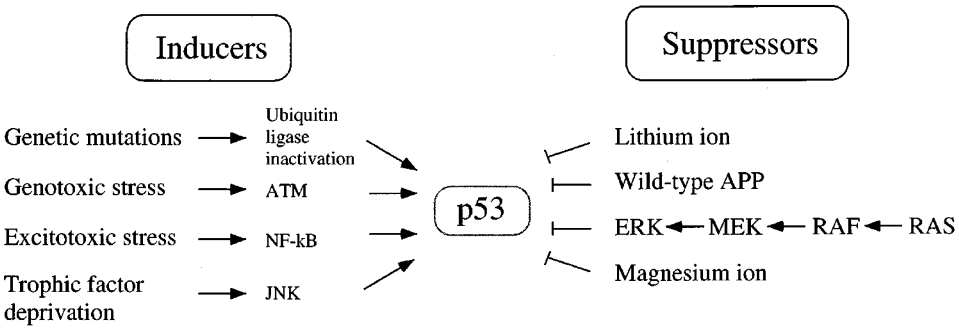

Figure 1 Schematic representation of proposed inducers and suppressors of p53 expression and p53-mediated cell death in neurons. Specific cellular insults such as genotoxic and excitotoxic stresses are shown in relation to the specific signal transduction cascades they activate upstream of p53. An inactivating mutation in the E6-AP ubiquitin ligase, in a mouse model of Angelman's syndrome, has been associated with increased cytoplasmic abundance of the p53 protein,[50] consistent with the demonstration that p53 protein levels are normally regulated through a ubiquitin-dependent, proteasome-mediated pathway.[10,11] The mechanisms by which the various suppressors limit p53 expression or function following injury have not been identified with the exception of the RAS→ERK pathway. ATM, ataxia telangiectasia gene; JNK, c-Jun-N-terminal kinase; APP, amyloid precursor protein; ERK, extracellular signal regulated kinase; MEK, mitogen activated protein kinase kinase

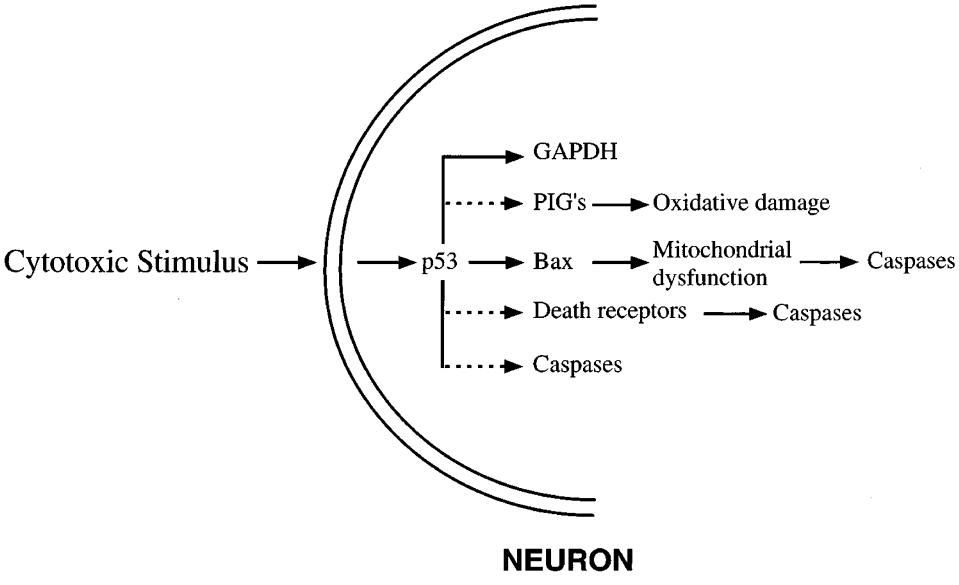

Figure 2 Schematic representation of cell death effectors activated in response to p53 induction. Various cytotoxic insults lead to the activation of p53 (as shown in Figure 1), which, in turn, activates several downstream effectors. Those pathways clearly associated with p53 dependent cell death in neurons are marked by solid arrows. Those pathways that have been associated with p53-dependent cell death in non-neuronal cells are marked by broken arrows. Clearly, many of the p53-dependent downstream effectors identified in non-neuronal cells should be evaluated in neurons. Caspases are listed in relation to several distinct pathways because evidence demonstrates that they are activated in response to: (1) mitochondrial damage and cytochrome c release; (2) the activation of death receptors such as TNF receptor and Fas (CD95); and (3) direct protein-protein interactions with p53.[21] GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PIG's, p53-inducible genes

neurons subject to DNA damage.[70] Antisense oligonucleotide-mediated suppression of GAPDH expression is neuroprotective,[148] suggesting that GAPDH may function as a p53 cell death effector. However, the precise mechanism underlying the involvement of GAPDH in neuronal apoptosis is unclear. Other genes, such as DR5, Fas, Fas ligand[18] and PERP[149] have been shown to be induced by apoptotic stimuli as a result of p53 activation in a variety of non-neuronal cell types, but the involvement of these genes in p53-dependent neuronal apoptosis is not known.

Summary

Emerging evidence obtained from acute injury models and brain tissue derived from patients with chronic neurodegenerative diseases implicate the p53 tumor suppressor protein in the regulation of neuronal cell death. The presence of p53 in damaged neurons, which often suffer significant oxidative stress following injury, is consistent with p53's known role in responding to a variety of stimuli, including oxidative stress, chemotherapeutic agents, hypoxia, nucleotide depletion, and oncogene expression.[114,150] Many unanswered questions remain regarding the role of p53 in neurons. For example, does p53 normally play a role in maintaining DNA integrity in neurons by regulating DNA repair processes in the absence of injury? How p53 induces neuronal cell death remains unresolved. The full gamut of genes activated or repressed in neurons in response to p53 induction have not been identified. In this regard, gene expression studies involving serial analysis of gene expression (SAGE) and cDNA microarray analysis will help to identify genes that are differentially expressed in response to p53 induction,[151] further defining the mechanisms underlying p53-dependent cell death in neurons. Characterizing the involvement of recently identified p53 family members in neuronal cell death will also contribute to the current understanding of the p53 pathway. All three proteins (p53, p63 and p73) share similar transcriptional activities as well as the ability to induce apoptosis.[152,153] However, each appears to play a distinct role in development and tumor suppression.[152,153] Additional evidence in support of a direct role for p53 in neuronal apoptosis will eventually be provided by the application of chemical inhibitors of p53,[89] which may be utilized to transiently suppress p53-mediated cell death pathways in acutely injured neurons. The continuing development of new information concerning p53-dependent neuronal cell death is encouraging, as this knowledge may ultimately be translated into effective treatments for maintaining neuronal viability and restoring function following cytopathic insults to the nervous system.

Note added in proof

After submission of this manuscript, two papers have appeared that are relevant to this review. Pozniak et al. (Science 289:304-306) have demonstrated in vivo and in vitro that an amino terminal-truncated form of p73 functions as a p53 antagonist, preventing p53-mediated developmental death of sympathetic neurons in response to NGF deprivation. Steffan et al. (Proc. Natl. Acad. Sci. USA 91:9842-9846) have shown that the Huntington's disease protein, huntingtin, interacts with p53 and CBP affecting p53-dependent gene transcription, providing another example of p53's potential contribution to neurodegenerative diseases.

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