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p53 Pro-Oxidant Activity in the Central Nervous System: Implication in Aging and Neurodegenerative Diseases

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Abstract

Recent advances in delineating the biological functions of p53 had shed the light on its key role in the multifacets of cellular homeostasis. After its activation, *via* DNA damage, oxidative stress, or aberrant expression of oncogenes, p53 transduces its classical effect through several mechanisms comprising activation of the DNA repair machinery, cell cycle arrest, and initiation of apoptosis or senescence. In the mammalian brain, p53 plays critical functions in normal development, tumor suppression, neurodegenerative diseases, and aging. Herein, we focus on the constitutive pro-oxidant activity of p53 in neurons and discuss the potential implication of this finding in the context of neurodegenerative diseases and normal brain aging. *Antioxid. Redox Signal.* 15, 1729–1737.

Introduction

AGING IS THE PRIME RISK FACTOR for the development of most neurodegenerative diseases. Although the exact reason for this is unknown, it is possible that specific neuronal genes having protective roles are downregulated in the aging brain due to increased mutational rate and/or defective DNA repair at their promoter (42). Neuronal cells also likely accumulate more mutations than most other cell types in their genomic DNA with age, leading to impaired cellular functions (30). One reason for this may be the inability of postmitotic cells to replicate their DNA, a process that is tightly coupled to DNA damage checkpoint and DNA repair (6, 52). Neurons also have a high metabolic activity and consume large amount of oxygen, and thus may be exposed to higher levels of oxidative stress than other tissues (30, 52). In turn, it is well known that DNA mutations, cellular oxidative damages, and cellular stresses in general can lead to activation of the p53 tumor suppressor gene. In this review, we will analyze the multiple evidences implicating p53 in the progression of neurodegenerative diseases. Moreover, the potential driving force of p53 in normal brain aging will be discussed, focusing on the constitutive pro-oxidant activity of p53 in neurons.

p53 in Brain Development and Cancer

The p53 gene family plays important functions in the regulation of proliferation, differentiation, and apoptosis in the central (CNS) and peripheral nervous system. Although *p53*-deficient mice are prone to develop a variety of tumors within the first 6 months of life, they apparently develop normally (20, 56). However, studies have showed that a fraction of *p53*-deficient embryos display exencephaly caused by an overgrowth of neural tissue in the midbrain and resulting in a neural tube closure defect (3, 13, 55). We also observed similar brain abnormalities in *p53*-deficient embryos (Fig. 1). This brain overgrowth phenotype probably results from reduced progenitor cells apoptosis, and resembles genetic deficiency in pro-apoptotic genes like Apaf-1 and caspase-9 (9, 29). Nonetheless, the majority of *p53*-deficient mice develop normally, possibly in part due to the compensatory effect of the two other p53 family members, that is, p63 and p73 (32). Still, overproliferation of neural stem cells located in the brain subventricular zone is consistently observed in *p53*-deficient adult mice, suggesting that *p53*-inactivating mutations may be important for the development of astrocytomas (28, 46). Hence, postnatal ablation of *p53* in neural stem cells and astrocytes of *p53* conditional mutant mice leads to the development of malignant astrocytomas (68). Finally, abnormalities in neuritogenesis have also been reported in cortical neurons of p53-deficient animals, uncovering a new function for p53 in postmitotic neurons development and maturation (26, 60).

p53 Is Pro-Apoptotic in the Nervous System

In the nervous system, p53 plays a pivotal role in the elimination of newly born postmitotic neurons that do not appropriately differentiate. Several studies have showed that p53 is involved in natural cell death of peripheral neurons of the sympathetic superior cervical ganglion early after birth (1, 2, 57). p53 can induce a programmed cell death-signaling

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FIG. 1. *p53*-deficient embryos display exencephaly. Photograph of wild-type and $p53^{-/-}$ embryos at embryonic stage 18.5. Note the general malformation of the head and the protuberance of the midbrain in the $p53^{-/-}$ embryo. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

cascade after nerve growth factor (NGF) withdrawal and/or p75 neurothrophin receptor activation (1). Overexpression of p53 is also sufficient to induce apoptosis of sympathetic neurons (34, 57). In contrast, inactivation of p53 in sympathetic neurons increases cell survival after NGF withdrawal (66). Finally, naturally occurring sympathetic neuronal death is also reduced in *p53* mutant mice (1).

p53 is a short-lived protein that is constantly degraded by the proteasome. However, when the cell is exposed to various stressors, p53 undergoes post-translational modifications such as phosphorylation and acetylation, allowing its stabilization and activation (39). Once activated, p53 can enhance or repress transcription of target genes. In the nervous system, numerous p53 targets, such as Bcl2-associated X protein (Bax), have been implicated in the induction of apoptosis (16, 72). *Apaf-1* is another direct target of p53, which, by forming the apoptosome, plays a pivotal role in the regulation of neuronal apoptosis after injury (27, 65). The two BH3-only proteins, NOXA (PMAIP1 [phorbol-12-myristate-13-acetate-induced protein 1]) and PUMA, are also important mediators of *p53*-dependent apoptosis (15, 37, 71). In cortical neurons, it was showed that apoptosis is independent of p53 accumulation at the mitochondria. Instead, apoptosis is exclusively induced through the transcription-dependent functions of p53. Unlike NOXA, PUMA is sufficient to induce Bax and ultimately neuronal cell death, and thus provides the critical link between p53 and Bax (16, 64).

p53 Is Pro-Oxidant in the Central Nervous System

The role of *p53* in organismal aging and cell oxidative metabolism remains highly controversial. In the aging rat brain, p53 gene and protein expression levels are increased (14, 21), and p53 hyperactivity can promote accelerated aging in animal models. For example, mice expressing a constitutively active form of p53 display a premature aging-like phenotype, and overexpression of the short isoform of p53 (p44) also leads to a phenotype of growth suppression and premature aging in mice (43, 63). In *Drosophila*, expression of a dominant negative form of p53 in adult CNS neurons, but not in other organs, extends lifespan and increases the resistance to paraquat (5). This finding is notable considering studies in flies and nematodes that suggest that neuronal functions are directly implicated in lifespan determination (69).

In contrast with these observations, it was showed that increasing the number of wild-type p53 alleles using a bacterial artificial chromosome in transgenic mice improves median lifespan and reduces tumor frequencies, possibly through increased expression of the antioxidant genes Sestrin 1 and 2 (Fig. 2) (45). The Sestrins are implicated in the regeneration of the antioxidant molecules Peroxiredoxins (7, 45, 48, 70). Similarly, p53 activity was shown to be protective in cultured fibroblasts under low stress conditions, apparently also through the activations of Sestrins (54). However, robust p53 activation after chronic insults or oncogenic stresses consistently results in the induction of apoptosis, in postmitotic neurons and cancer-prone dividing cells (Fig. 2). In some instance, dividing cells can also proceed through the alternative route of senescence.

In the brain, one-way p53 may be involved in the control of neuronal aging may be link to its function on reactive oxygen species (ROS) metabolism. A robust and persistent induction of p53, suggesting a relatively high stress level, results in activation of the pro-oxidant genes PIG3, Proline Oxidase, PUMA, and P66SHC and in ROS production (Fig. 2) (41, 51, 53, 61, 67). At the same time, several studies have shown that p53 can directly repress antioxidant genes to enhance ROS production, possibly to facilitate apoptosis induction (Fig. 2). p53 can repress *SOD2* expression at the promoter level by interacting with SP1 (18, 22). p53 can also repress phase II antioxidant response (AOR) genes, which are normally activated by the Nrf2 (NFE2L2 [nuclear factor (erythroid-derived 2)-like 2]) transcription factor (25). The phase II AOR genes encode antioxidant proteins such as glutathione S-transferase α1, NAD(P)H quinone oxidoreductase, and cystine/glutamate transporter (25). We have shown that in the pathological context of *Bmi1*-deficiency, p53 can repress the expression of several AOR genes as well as *SOD2* in cortical neurons. p53 association to these promoters correlated with the accumulation of corepressor complexes containing nuclear receptor corepressor 1 and histone deacetylase 1 (HDAC1), and with the presence of histone marks indicative of a repressed chromatin state (10). Most surprisingly, analysis of *p53*-null mice and cultured neurons revealed that p53 also represses expression of AOR genes and *SOD1* in physiological conditions (Fig. 3A). In the brain of adult *p53*-null mice, we also observed lower accumulation of lipid peroxidation adducts compared with wild-type littermates (Fig. 3B). These data suggest that p53 activity promotes oxidative damages accumulation in cortical neurons even in physiological conditions.

The Activity of p53 on the Oxidative Metabolism Is Context-Dependent

As presented above, the overall effect of *p53* deficiency on the cellular oxidative metabolism is apparently context dependent. This is reflected by the seemingly opposite effect of *p53* deficiency on the oxidative metabolism of neurons *versus* mouse embryonic lung fibroblasts (MELFs) (10, 45, 54). While p53 is pro-oxidant is neurons, p53 is overall antioxidant in

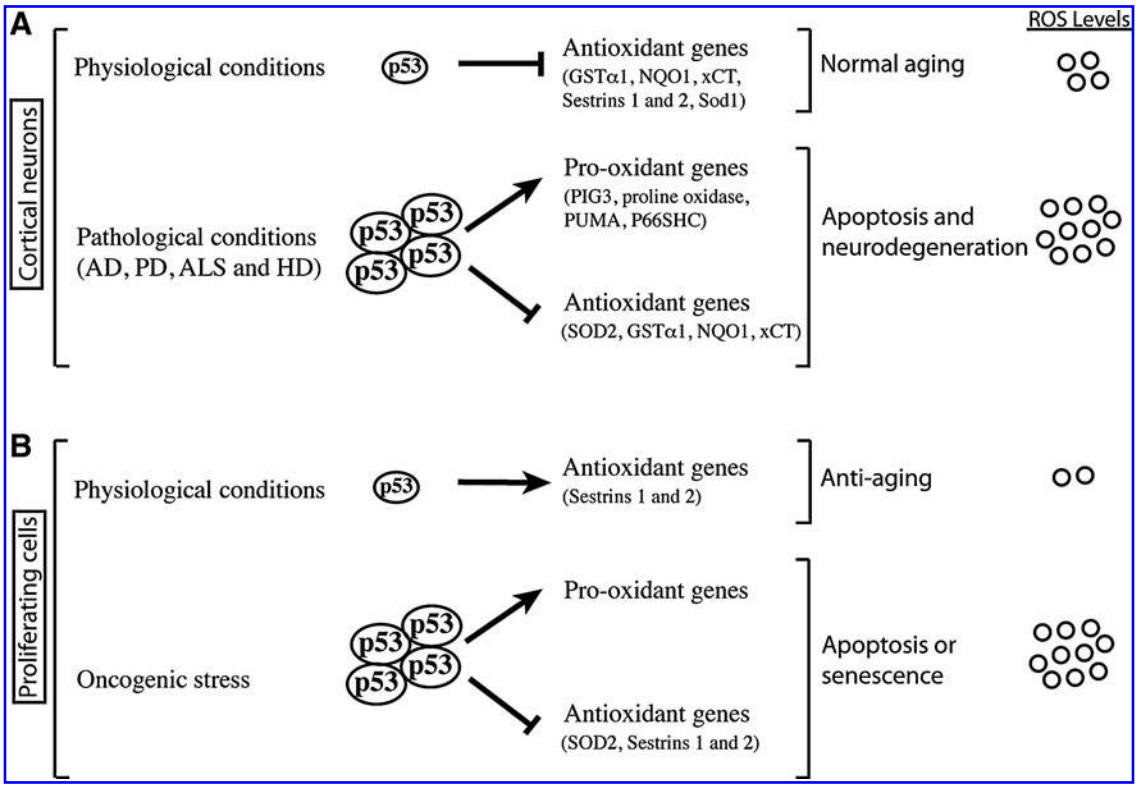

FIG. 2. p53 is pro-oxidant in neurons under physiological conditions. (A) Under physiological conditions, low p53 activities are pro-oxidant in cortical neurons (and possibly also in other types of postmitotic cells) through direct repression of several antioxidant genes. Under chronic insults or pathological conditions, p53 responds by pushing further the cell oxidative balance toward a pro-oxidant state. This cellular state, characteristic of neurodegenerative diseases, is favored by the dual action of p53 as an activator of pro-oxidant genes, and a repressor of antioxidant genes. **(B)** In proliferating cells, such as mouse embryonic lung fibroblasts or adult liver cells, p53 is antioxidant under physiological conditions. This may allow protection of the genome against DNA damage accumulation. When the cells are challenged by an oncogenic stress, p53 activity than switched toward a pro-oxidant status. This catalyzed senescence or apoptotic pathways that protect the organism against cancer initiation.

MELFs. The same observations were made *in vivo* when we compared the oxidative status in the brain, liver, and lungs of *p53*-null mice (Fig. 3A). Others groups have also demonstrated that p53 possesses an antioxidant function in mouse embryonic fibroblasts (MEFs), where MEFs with an extra copy of *p19* and *p53* show increased expression of Sestrins (45, 54). Likewise, reduced glutathione levels were found in the liver of mice with an extra copy of *p19* and *p53*, suggesting a global increase in antioxidant activity. On the other hand, loss of *p53* promotes the elevation of intracellular ROS concen-

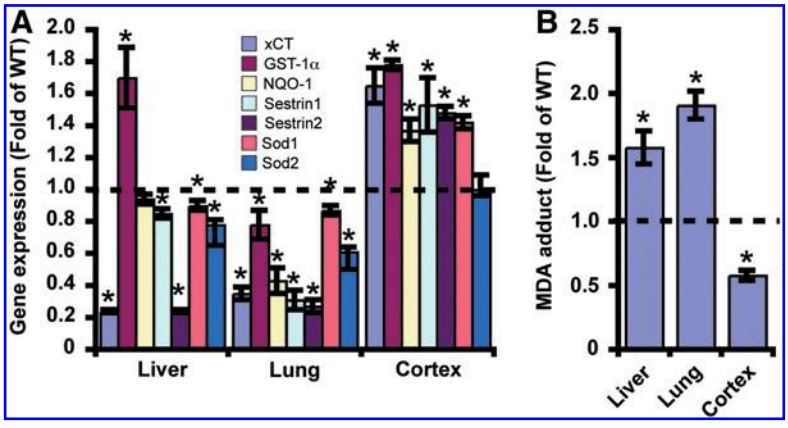

FIG. 3. *p53* is pro-oxidant in central nervous system. (A) Q-PCR analysis of antioxidant gene expression levels in p53 mutant mice liver, lung, and cortex. Note that expression of most antioxidant genes is increased in the brain of p53 mutants, in contrast with the liver and lungs. Data are represented as fold change relative to wild-type samples, which were set at 1 (*dashed line*). Results are mean SD ($n = 3$–4; $^*p < 0.05$). **(B)**. Lipid peroxidation was measured in p53 mutant mice liver, lung, and cortex homogenates as concentration of MDA. Lipid peroxidation is significantly reduced in the brain of p53 mutants. Data were normalized to sample protein contents and are represented as fold change relative to wild-type samples, which were set at 1 (dashed line). Results are mean ± SD ($n = 3$–5; $^*p < 0.05$). Adapted from Chatoo *et al.* (10). (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

tration and DNA damage accumulation (54). These findings suggest that the primary function of *p53* in most organs consists of protecting the organism from cancer initiation by reducing intracellular ROS concentrations and thus preventing DNA damage accumulation. An obvious question arising from these observations is why under physiological conditions p53 does not also protect neurons from oxidative damage accumulation by lowering intracellular ROS levels? At first glance, this would appear highly beneficial for neurons. Hence, these findings may indicate that p53 pro-oxidant activity plays still uncharacterized biological functions in neurons that are important for synaptic activity, long-term potentiation, or neuronal plasticity.

To date however, the molecular basis of these paradoxical observations is unknown. One proposed mechanism to explain the cell-specific effects of p53 on the regulation of ROS metabolism is linked to the threshold level of stress required to activate p53 in each cell type. For instance, in MEFs and various organs (in the absence of exogenous stress), low level of p53 is sufficient to induce expression of antioxidants genes, such as the Sestrins (54). However, in conditions of severe or chronic stress, p53 is activated and accumulates to become pro-oxidant and pro-apoptotic (54). In postmitotic neurons, the levels of stress required to activate the pro-oxidant function of p53 would be much lower in comparison with other tissues. In this model, p53 would always remain pro-oxidant in neurons. This model, however, somewhat implies that other proteins involved in stress response or p53 regulation are hyperactive in neurons.

Herein, we propose several alternate molecular mechanisms that could explain the cell type-specific function of p53 on the oxidative metabolism (Fig. 4). (A) In mature neurons, p53 can repress transcription of AOR genes through the recruitment of corepressor complexes containing HDAC and N-CoR (10). In this tissue-specific corepressor model, corepressors preferentially expressed in neurons, such as N-CoR or mSin3a, would recruit HDACs to form a complex with p53 at AOR gene promoters (Fig. 4A). This type of regulation has been documented earlier (47, 74). (B) The tissue-specific function of p53 may be also explained by the finding of a novel type of p53 DNA binding elements present on promoters. The DNA binding elements of p53 on the promoter of AOR genes could be atypical (25). In this bivalent promoter model, two DNA binding elements located on the promoter can determine the fate of p53 as an activator or as a repressor (Fig. 4B). In MELFs, the repressor-binding site of p53 would be normally occupied by a putative interfering protein (protein X), thus forcing p53 to bind to the activator site. In neurons, the absence of this interfering protein would allow p53 to preferentially bind to the repressive binding element (33). (C) Another mechanism that implicates a stress sensor model can be proposed to explain the function of p53. In proliferating cells, the risk of DNA errors occurrence during the process of DNA replication is elevated when compared with neurons, which are postmitotic. One hypothesis is that in MELFs, DNA damage induces specific modifications in p53 leading to its preferential interaction with coactivators, thus enhancing its transactivation potential. In neurons, however, where oxidative stress is predominant, p53 is also activated but associate preferentially with corepressors (Fig. 4C). Some studies have highlighted this type of regulation in the context of cellular hypoxia (38). (D) Another proposed model is

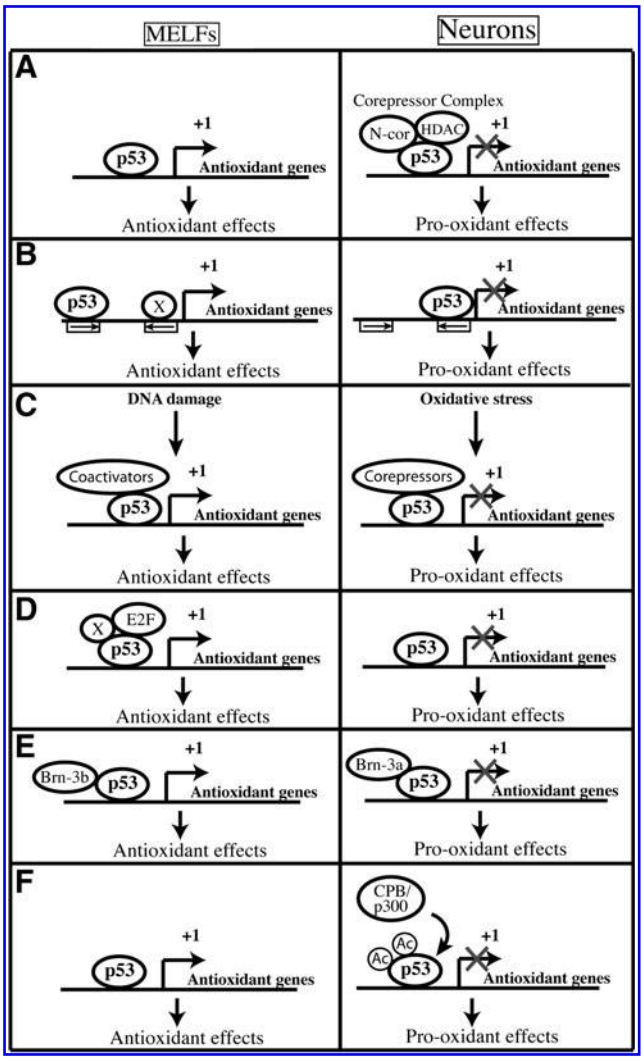

FIG. 4. p53 activity on the cellular oxidative metabolism is context-dependent. The activity of p53 on the cellular oxidative metabolism is context-dependent. While p53 is pro-oxidant in neurons (and possibly also in other postmitotic cells), it displays antioxidant effects in mouse embryonic lung fibroblasts (and possibly also in most other dividing cells). These paradoxical activities can be explained by several mechanisms (see text for details). Proposed models are presented herein **(A–F)**. These processes are probably not mutually exclusive. MELF, mouse embryonic lung fibroblast.

based on the postmitotic nature of neurons. In this cell cycle-dependent model, factors only present in dividing cells, such as members of the Rb/E2F pathway, for example, would associate with p53 to form a coactivator complex (Fig. 4D) (11). This association would not be present in neurons, allowing for constitutive AOR genes repression by p53. (E) An alternative mechanism to explain the dual function of p53 may be through tissue-specific expression of highly related transcription cofactors (Fig. 4E). In this tissue-specific cofactor model, the Pou4f1 (BRN3A) POU domain, class 4, transcription factor 1 (Brn-3a), and Pou4f2 (BRN3B) POU domain, class 4, transcription factor 2 (Brn-3b) transcription factors have opposite and antagonistic effects toward p53. Brn-3a promotes p53-mediated gene repression, whereas

Brn-3b cooperates with p53 to activate the expression of the same target genes (8). (F) The last proposed model is the tissue-specific post-translation model and involves cell type-specific expression of a factor that would induce post-translational modifications of p53, leading to its activation beyond the threshold level (Fig. 4F). For example, the transcriptional cofactor CBP/p300 can acetylate p53 and induces its activation (17). p53 acetylation is critical for its activation (59).

p53, Aging, and Neurodegenerative Diseases

Aging is a multifactorial process. One grand theory of aging stipulates that progressive imbalance between mitochondria-based ROS production and the antioxidant defense system is the cause of cellular and organismal aging. The action of excessive ROS concentrations would lead to DNA damage, protein nitrosylation, and lipid peroxidation accumulations, ultimately affecting the entire cell metabolism (30, 31). This scenario may be especially true in the brain, where neurons regenerative capacity is most limited and metabolic activity very high. The free radical theory of aging thus proposes an appealing explanation for the age-associated apparition of neurodegenerative diseases. The pro-oxidant behavior of p53 in neurons under both physiologic and pathologic conditions might enhance damage accumulation in the CNS and directly influences the aging process. In turn, DNA damages can induce p53 activation, possibly leading to the initiation of a vicious circle. Notably, although mice carrying extra copies of *p19^{Arf}* and *p53* have an increased medium lifespan, their maximum lifespan is not improved. This indicates that the p19/p53 pathway might not repress all the causes of physiological aging or that increasing p53 activity in the brain precludes lifespan extension (45). In-depth analysis of the brain of *p19/p53* transgenic mice could provide critical answers on the impact of increasing p53 activity on normal brain aging.

Neuronal dysfunctions due to the accumulation of mitochondria-associated oxidative damages are hallmark of age-related neurodegenerative diseases (40). Surprisingly, p53 seems to be the common troublemaker in these pathologies (Fig. 5). For example, several studies have shown that p53 expression is elevated in the Alzheimer disease (AD) brain (19, 49). Most surprisingly, the intracellular β-amyloid$_{42}$ peptide, which is associated with AD, can directly bind and activate the *p53* promoter, resulting in p53-dependent neuronal apoptosis (49). In contrast, inhibition of p53 prevents neuronal cell death induced by β-amyloid$_{1-42}$ (73). Several other neurodegenerative diseases have been linked to oxidative stress and mitochondrial dysfunction, resulting in p53-dependent neuronal cell death. For instance, in Parkinson disease, p53 can be a target of the nuclear enzyme Poly (ADP-ribose) polymerase 1, which is activated after DNA damages induced by 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) treatment (44). The poly-ADP-ribosylation of p53 leads to its stabilization and neuronal cell death. MPTP treatment can also induce activation of the p38 mitogen-activated protein kinase, resulting in p53 phosphorylation and neuronal apoptosis (36). Accordingly, *p53*-null mice or mice treated with p53 inhibitors are resistant to MPTP-induced dopaminergic neurons apoptosis (23, 50). Other studies have revealed that mutant Huntingtin (*Htt*), the mutated gene product in Huntington disease, binds to p53 and enhances p53 nuclear levels in neurons, and that genetic deletion of p53 suppresses neurobehavioral abnormalities of mutant *Htt-Tg* mice (4). Finally, p53 may also play a role in oxidative stress-induced cell death of motor neurons in amyotrophic lateral sclerosis (24). Taken together, these observations indicate that the inherent pro-oxidant and pro-apoptotic activities of p53 in neurons operate as progression factors in the natural process of brain aging and development of aged-related neurodegenerative diseases.

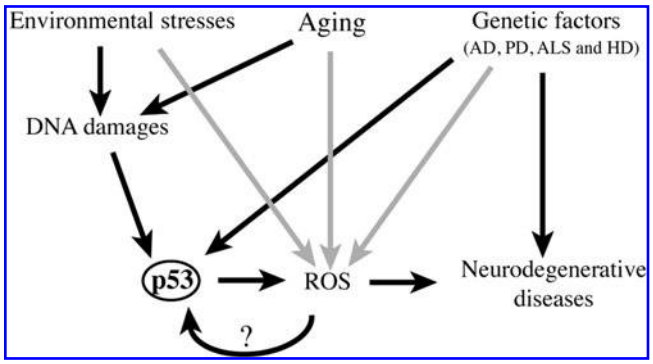

FIG. 5. p53 is linked to normal brain aging and neurodegenerative diseases. The cumulative action of increasing ROS concentrations was proposed to be the central mechanism of cellular and organismal aging. Abnormal ROS metabolism and ROS-related cellular damages are also found in several aged-related neurodegenerative diseases. In this triad (ROS, aging, and neurodegenerative diseases), p53 is thought to be the main regulatory player. ROS, reactive oxygen species.

Clinical Implications

The clinical implications of the reported roles of p53 in neurodegenerative diseases are potentially very important. Can we delay or attenuate the progression of neurodegenerative diseases by inhibiting p53 pro-apoptotic and pro-oxidant activities? The answer is probably yes. However, the critical function of p53 in preventing cancer initiation in most organs as well as in brain astrocytes and neural stem cells must be considered (Fig. 6). Hence, partial inhibition of p53 only in the brain appears as the safest option. However, considering the advance age of most affected patients, systemic inhibition of p53 is unlikely to allow cancer initiation and development within the expected remaining lifetime. Inhibitors of p53 activity have been developed and tested in animal models of Parkinson and Huntington disease. Notably, reported results were quite spectacular. However, the promise of these discoveries for the treatment of patients is still awaited. Alternatively, antioxidant treatment may be use to directly reduce cellular oxidative stress, which is common is most neurodegenerative disease. A large clinical trial using coenzyme Q10 as a food supplement is undergoing in patients suffering from Huntington disease (Huntington Study Group). Alternatively, a more invasive approach aiming to overexpress antioxidant-activating factors such as PGC1α or Nrf2 in neurons using a virus can be envisaged (35, 58). However, targeting large numbers of brain neurons with this approach will be difficult. Rather, injection of primary human

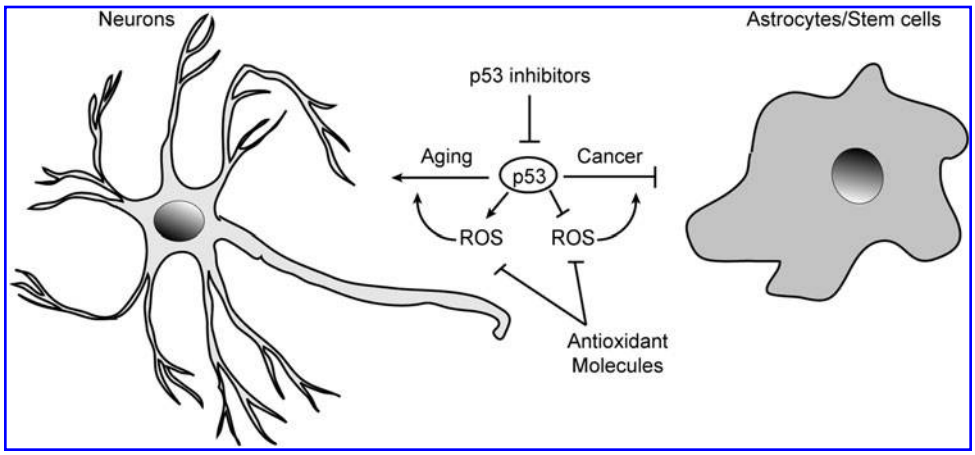

FIG. 6. Clinical applications. In postmitotic neurons of the brain, inhibition of p53 activity is predicted to be beneficial against accumulation of ROS-mediated cellular damages. This is especially true in the context of normal aging. In the context of neurodegenerative diseases, p53 inhibition would also counteract p53-mediated apoptosis. A possible drawback of this strategy is the possible initiation of cellular transformation in astrocytes and neural stem cells, where p53 operates as a guardian of the genome. In these cells, p53 can reduce ROS-mediated DNA damage accumulation or induce apoptosis upon oncogenic signaling. A possible alternative to p53 inhibition is the use of antioxidant molecules, which can in principle counteract the pathological action of ROS in neurons without affecting p53 antioncogenic activity.

fibroblasts engineered to secrete survival or growth factors such as NGF appears more feasible (62). Similarly, mouse astrocytes that overexpress Nrf2 can protect dopaminergic neurons from MPTP cytotoxicity by a cell nonautonomous mechanism (12).

Concluding Remarks

The *p53* gene is activated in most neurodegenerative diseases and is possibly a driving force of normal brain aging. The role of *p53* in protecting the genome from mutagenic oxidative damage and against cellular transformation in most organs, including dividing brain cells, is most likely predominant in term of species evolution and fitness compare to its constitutive pro-oxidant and pro-aging activity in brain neurons. Hence, brain aging, age-related cognitive decline, and AD may be regard as a recent evolutionary curiosity owing to the unprecedented longevity of the human specie. Finally, it may be wise to attempt to delay normal brain aging and thus the onset of neurodegenerative diseases by combining a healthy diet rich in polyphenols, caloric restriction, exercise, and mental activity. The awaited discovery of the Fontaine de Jouvence molecule is the last salvation for those not quite convinced by this prescription.

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References

1. Aloyz RS, Bamji SX, Pozniak CD, Toma JG, Atwal J, Kaplan DR, and Miller FD. p53 is essential for developmental neuron death as regulated by the TrkA and p75 neurotrophin receptors. *J Cell Biol* 143: 1691–1703, 1998.
2. Anderson CN and Tolkovsky AM. A role for MAPK/ERK in sympathetic neuron survival: protection against a p53-dependent, JNK-independent induction of apoptosis by cytosine arabinoside. *J Neurosci* 19: 664–673, 1999.
3. Armstrong JF, Kaufman MH, Harrison DJ, and Clarke AR. High-frequency developmental abnormalities in p53-deficient mice. *Curr Biol* 5: 931–936, 1995.
4. Bae BI, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, Hayward SD, Moran TH, Montell C, Ross CA, Snyder SH, and Sawa A. p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. *Neuron* 47: 29–41, 2005.
5. Bauer JH, Poon PC, Glatt-Deeley H, Abrams JM, and Helfand SL. Neuronal expression of p53 dominant-negative proteins in adult *Drosophila melanogaster* extends life span. *Curr Biol* 15: 2063–2068, 2005.
6. Bielas JH and Heddle JA. Proliferation is necessary for both repair and mutation in transgenic mouse cells. *Proc Natl Acad Sci U S A* 97: 11391–11396, 2000.
7. Budanov AV, Sablina AA, Feinstein E, Koonin EV, and Chumakov PM. Regeneration of peroxiredoxins by p53-regulated sestrins, homologs of bacterial AhpD. *Science* 304: 596–600, 2004.
8. Budhram-Mahadeo VS, Bowen S, Lee S, Perez-Sanchez C, Ensor E, Morris PJ, and Latchman DS. Brn-3b enhances the pro-apoptotic effects of p53 but not its induction of cell cycle arrest by cooperating in trans-activation of bax expression. *Nucleic Acids Res* 34: 6640–6652, 2006.
9. Cecconi F, Alvarez-Bolado G, Meyer BI, Roth KA, and Gruss P. Apaf1 (CED-4 homolog) regulates programmed cell death in mammalian development. *Cell* 94: 727–737, 1998.
10. Chatoo W, Abdouh M, David J, Champagne MP, Ferreira J, Rodier F, and Bernier G. The polycomb group gene Bmi1 regulates antioxidant defenses in neurons by repressing p53 pro-oxidant activity. *J Neurosci* 29: 529–542, 2009.
11. Chen D, Pacal M, Wenzel P, Knoepfler PS, Leone G, and Bremner R. Division and apoptosis of E2f-deficient retinal progenitors. *Nature* 462: 925–929, 2009.
12. Chen PC, Vargas MR, Pani AK, Smeyne RJ, Johnson DA, Kan YW, and Johnson JA. Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: Critical role for the astrocyte. *Proc Natl Acad Sci U S A* 106: 2933–2938, 2009.
13. Choi J and Donehower LA. p53 in embryonic development: maintaining a fine balance. *Cell Mol Life Sci* 55: 38–47, 1999.

14. Chung YH, Shin C, Kim MJ, Lee B, Park KH, and Cha CI. Immunocytochemical study on the distribution of p53 in the hippocampus and cerebellum of the aged rat. *Brain Res* 885: 137–141, 2000.
15. Cregan SP, Arbour NA, Maclaurin JG, Callaghan SM, Fortin A, Cheung EC, Guberman DS, Park DS, and Slack RS. p53 activation domain 1 is essential for PUMA upregulation and p53-mediated neuronal cell death. *J Neurosci* 24: 10003–10012, 2004.
16. Cregan SP, MacLaurin JG, Craig CG, Robertson GS, Nicholson DW, Park DS, and Slack RS. Bax-dependent caspase-3 activation is a key determinant in p53-induced apoptosis in neurons. *J Neurosci* 19: 7860–7869, 1999.
17. Culmsee C and Mattson MP. p53 in neuronal apoptosis. *Biochem Biophys Res Commun* 331: 761–777, 2005.
18. Dhar SK, Xu Y, Chen Y, and St. Clair DK. Specificity protein 1-dependent p53-mediated suppression of human manganese superoxide dismutase gene expression. *J Biol Chem* 281: 21698–21709, 2006.
19. Di Domenico F, Cenini G, Sultana R, Perluigi M, Uberti D, Memo M, and Butterfield DA. Glutathionylation of the pro-apoptotic protein p53 in Alzheimer's disease brain: implications for AD pathogenesis. *Neurochem Res* 34: 727–733, 2009.
20. Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery CA, Jr., Butel JS, and Bradley A. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature* 356: 215–221, 1992.
21. Dorszewska J and Adamczewska-Goncerzewicz Z. Oxidative damage to DNA, p53 gene expression and p53 protein level in the process of aging in rat brain. *Respir Physiol Neurobiol* 139: 227–236, 2004.
22. Drane P, Bravard A, Bouvard V, and May E. Reciprocal down-regulation of p53 and SOD2 gene expression-implication in p53 mediated apoptosis. *Oncogene* 20: 430–439, 2001.
23. Duan W, Zhu X, Ladenheim B, Yu QS, Guo Z, Oyler J, Cutler RG, Cadet JL, Greig NH, and Mattson MP. p53 inhibitors preserve dopamine neurons and motor function in experimental parkinsonism. *Ann Neurol* 52: 597–606, 2002.
24. Eve DJ, Dennis JS, and Citron BA. Transcription factor p53 in degenerating spinal cords. *Brain Res* 1150: 174–181, 2007.
25. Faraonio R, Vergara P, Di Marzo D, Pierantoni MG, Napolitano M, Russo T, and Cimino F. p53 suppresses the Nrf2-dependent transcription of antioxidant response genes. *J Biol Chem* 281: 39776–39784, 2006.
26. Ferron SR, Marques-Torrejon MA, Mira H, Flores I, Taylor K, Blasco MA, and Farinas I. Telomere shortening in neural stem cells disrupts neuronal differentiation and neuritogenesis. *J Neurosci* 29: 14394–14407, 2009.
27. Fortin A, Cregan SP, MacLaurin JG, Kushwaha N, Hickman ES, Thompson CS, Hakim A, Albert PR, Cecconi F, Helin K, Park DS, and Slack RS. APAF1 is a key transcriptional target for p53 in the regulation of neuronal cell death. *J Cell Biol* 155: 207–216, 2001.
28. Gil-Perotin S, Marin-Husstege M, Li J, Soriano-Navarro M, Zindy F, Roussel MF, Garcia-Verdugo JM, and Casaccia-Bonnefil P. Loss of p53 induces changes in the behavior of subventricular zone cells: implication for the genesis of glial tumors. *J Neurosci* 26: 1107–1116, 2006.
29. Hakem R, Hakem A, Duncan GS, Henderson JT, Woo M, Soengas MS, Elia A, de la Pompa JL, Kagi D, Khoo W, Potter J, Yoshida R, Kaufman SA, Lowe SW, Penninger JM, and Mak TW. Differential requirement for caspase 9 in apoptotic pathways *in vivo*. *Cell* 94: 339–352, 1998.
30. Halliwell B. Oxidative stress and neurodegeneration: where are we now? *J Neurochem* 97: 1634–1658, 2006.
31. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 11: 298–300, 1956.
32. Jacobs WB, Kaplan DR, and Miller FD. The p53 family in nervous system development and disease. *J Neurochem* 97: 1571–1584, 2006.
33. Johnson RA, Ince TA, and Scotto KW. Transcriptional repression by p53 through direct binding to a novel DNA element. *J Biol Chem* 276: 27716–27720, 2001.
34. Jordan J, Galindo MF, Prehn JH, Weichselbaum RR, Beckett M, Ghadge GD, Roos RP, Leiden JM, and Miller RJ. p53 expression induces apoptosis in hippocampal pyramidal neuron cultures. *J Neurosci* 17: 1397–1405, 1997.
35. Kanninen K, Heikkinen R, Malm T, Rolova T, Kuhmonen S, Leinonen H, Ylä-Herttuala S, Tanila H, Levonen AL, Koistinaho M, and Koistinaho J. Intrahippocampal injection of a lentiviral vector expressing Nrf2 improves spatial learning in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* 106: 16505–16510, 2009.
36. Karunakaran S, Saeed U, Mishra M, Valli RK, Joshi SD, Meka DP, Seth P, and Ravindranath V. Selective activation of p38 mitogen-activated protein kinase in dopaminergic neurons of substantia nigra leads to nuclear translocation of p53 in 1-methyl-4-phenyl-1, 2,3, 6-tetrahydropyridine-treated mice. *J Neurosci* 28: 12500–12509, 2008.
37. Kiryu-Seo S, Hirayama T, Kato R, and Kiyama H. Noxa is a critical mediator of p53-dependent motor neuron death after nerve injury in adult mouse. *J Neurosci* 25: 1442–1447, 2005.
38. Koumenis C, Alarcon R, Hammond E, Sutphin P, Hoffman W, Murphy M, Derr J, Taya Y, Lowe SW, Kastan M, and Giaccia A. Regulation of p53 by hypoxia: dissociation of transcriptional repression and apoptosis from p53-dependent transactivation. *Mol Cell Biol* 21: 1297–1310, 2001.
39. Kruse JP and Gu W. Modes of p53 regulation. *Cell* 137: 609–622, 2009.
40. Lin MT and Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443: 787–795, 2006.
41. Liu Z, Lu H, Shi H, Du Y, Yu J, Gu S, Chen X, Liu KJ, and Hu CA. PUMA overexpression induces reactive oxygen species generation and proteasome-mediated stathmin degradation in colorectal cancer cells. *Cancer Res* 65: 1647–1654, 2005.
42. Lu T, Pan Y, Kao SY, Li C, Kohane I, Chan J, and Yankner BA. Gene regulation and DNA damage in the ageing human brain. *Nature* 429: 883–891, 2004.
43. Maier B, Gluba W, Bernier B, Turner T, Mohammad K, Guise T, Sutherland A, Thorner M, and Scrable H. Modulation of mammalian life span by the short isoform of p53. *Genes Dev* 18: 306–319, 2004.
44. Mandir AS, Simbulan-Rosenthal CM, Poitras MF, Lumpkin JR, Dawson VL, Smulson ME, and Dawson TM. A novel *in vivo* post-translational modification of p53 by PARP-1 in MPTP-induced parkinsonism. *J Neurochem* 83: 186–192, 2002.
45. Matheu A, Maraver A, Klatt P, Flores I, Garcia-Cao I, Borras C, Flores JM, Vina J, Blasco MA, and Serrano M. Delayed ageing through damage protection by the Arf/p53 pathway. *Nature* 448: 375–379, 2007.
46. Meletis K, Wirta V, Hede SM, Nister M, Lundeberg J, and Frisen J. p53 suppresses the self-renewal of adult neural stem cells. *Development* 133: 363–369, 2006.
47. Murphy M, Ahn J, Walker KK, Hoffman WH, Evans RM, Levine AJ, and George DL. Transcriptional repression by wild-type p53 utilizes histone deacetylases, mediated by interaction with mSin3a. *Genes Dev* 13: 2490–2501, 1999.

48. Neumann CA, Krause DS, Carman CV, Das S, Dubey DP, Abraham JL, Bronson RT, Fujiwara Y, Orkin SH, and Van Etten RA. Essential role for the peroxiredoxin Prdx1 in erythrocyte antioxidant defence and tumour suppression. *Nature* 424: 561–565, 2003.
49. Ohyagi Y, Asahara H, Chui DH, Tsuruta Y, Sakae N, Miyoshi K, Yamada T, Kikuchi H, Taniwaki T, Murai H, Ikezoe K, Furuya H, Kawarabayashi T, Shoji M, Checler F, Iwaki T, Makifuchi T, Takeda K, Kira J, and Tabira T. Intracellular Abeta42 activates p53 promoter: a pathway to neurodegeneration in Alzheimer's disease. *FASEB J* 19: 255–257, 2005.
50. Perier C, Tieu K, Guégan C, Caspersen C, Jackson-Lewis V, Carelli V, Martinuzzi A, Hirano M, Przedborski S, and Vila M. Two molecular pathways initiate mitochondria-dependent dopaminergic neurodegeneration in experimental Parkinson's disease. *Proc Natl Acad Sci U S A* 104: 8161–8166, 2007.
51. Polyak K, Xia Y, Zweier JL, Kinzler KW, and Vogelstein B. A model for p53-induced apoptosis. *Nature* 389: 300–305, 1997.
52. Rass U, Ahel I, and West SC. Defective DNA repair and neurodegenerative disease. *Cell* 130: 991–1004, 2007.
53. Rivera A and Maxwell SA. The p53-induced gene-6 (proline oxidase) mediates apoptosis through a calcineurin-dependent pathway. *J Biol Chem* 280: 29346–29354, 2005.
54. Sablina AA, Budanov AV, Ilyinskaya GV, Agapova LS, Kravchenko JE, and Chumakov PM. The antioxidant function of the p53 tumor suppressor. *Nat Med* 11: 1306–1313, 2005.
55. Sah VP, Attardi LD, Mulligan GJ, Williams BO, Bronson RT, and Jacks T. A subset of p53-deficient embryos exhibit exencephaly. *Nat Genet* 10: 175–180, 1995.
56. Sansom OJ and Clarke AR. p53 null mice: damaging the hypothesis? *Mutat Res* 452: 149–162, 2000.
57. Slack RS, Belliveau DJ, Rosenberg M, Atwal J, Lochmüller H, Aloyz R, Haghighi A, Lach B, Seth P, Cooper E, and Miller FD. Adenovirus-mediated gene transfer of the tumor suppressor, p53, induces apoptosis in postmitotic neurons. *J Cell Biol* 135: 1085–1096, 1996.
58. St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jäger S, Handschin C, Zheng K, Lin J, Yang W, Simon DK, Bachoo R, and Spiegelman BM. Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* 127: 397–408, 2006.
59. Tang Y, Zhao W, Chen Y, Zhao Y, and Gu W. Acetylation is indispensable for p53 activation. *Cell* 133: 612–626, 2008.
60. Tedeschi A, Nguyen T, Steele SU, Feil S, Naumann U, Feil R, and Di Giovanni S. The tumor suppressor p53 transcriptionally regulates cGKI expression during neuronal maturation and is required for cGMP-dependent growth cone collapse. *J Neurosci* 29: 15155–15160, 2009.
61. Trinei M, Giorgio M, Cicalese A, Barozzi S, Ventura A, Migliaccio E, Milia E, Padura IM, Raker VA, Maccarana M, Petronilli V, Minucci S, Bernardi P, Lanfrancone L, and Pelicci PG. A p53-p66Shc signalling pathway controls intracellular redox status, levels of oxidation-damaged DNA and oxidative stress-induced apoptosis. *Oncogene* 21: 3872–3878, 2002.
62. Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, and Conner J. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nat Med* 11: 551–555, 2005.
63. Tyner SD, Venkatachalam S, Choi J, Jones S, Ghebranious N, Igelmann H, Lu X, Soron G, Cooper B, Brayton C, Hee Park S, Thompson T, Karsenty G, Bradley A, and Donehower LA. p53 mutant mice that display early ageing-associated phenotypes. *Nature* 415: 45–53, 2002.
64. Uo T, Kinoshita Y, and Morrison RS. Apoptotic actions of p53 require transcriptional activation of PUMA and do not involve a direct mitochondrial/cytoplasmic site of action in postnatal cortical neurons. *J Neurosci* 27: 12198–12210, 2007.
65. Vaughn AE and Deshmukh M. Essential postmitochondrial function of p53 uncovered in DNA damage-induced apoptosis in neurons. *Cell Death Diff* 14: 973–981, 2007.
66. Vogel KS and Parada LF. Sympathetic neuron survival and proliferation are prolonged by loss of p53 and neurofibromin. *Mol Cell Neurosci* 11: 19–28, 1998.
67. Vousden KH and Ryan KM. p53 and metabolism. *Nat Rev Cancer* 9: 691–700, 2009.
68. Wang Y, Yang J, Zheng H, Tomasek GJ, Zhang P, McKeever PE, Lee EY, and Zhu Y. Expression of mutant p53 proteins implicates a lineage relationship between neural stem cells and malignant astrocytic glioma in a murine model. *Cancer Cell* 15: 514–526, 2009.
69. Wolkow CA. Life span: getting the signal from the nervous system. *Trends Neurosci* 25: 212–216, 2002.
70. Wood ZA, Schroder E, Robin Harris J, and Poole LB. Structure, mechanism and regulation of peroxiredoxins. *Trends Biochem Sci* 28: 32–40, 2003.
71. Wyttenbach A and Tolkovsky AM. The BH3-only protein Puma is both necessary and sufficient for neuronal apoptosis induced by DNA damage in sympathetic neurons. *J Neurochem* 96: 1213–1226, 2006.
72. Xiang H, Kinoshita Y, Knudson CM, Korsmeyer SJ, Schwartzkroin PA, and Morrison RS. Bax involvement in p53-mediated neuronal cell death. *J Neurosci* 18: 1363–1373, 1998.
73. Zhang Y, McLaughlin R, Goodyer C, and LeBlanc A. Selective cytotoxicity of intracellular amyloid beta peptide1–42 through p53 and Bax in cultured primary human neurons. *J Cell Biol* 156: 519–529, 2002.
74. Zilfou JT, Hoffman WH, Sank M, George DL, and Murphy M. The corepressor mSin3a interacts with the proline-rich domain of p53 and protects p53 from proteasome-mediated degradation. *Mol Cell Biol* 21: 3974–3985, 2001.

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Abbreviations Used

AD = Alzheimer disease
AOR = antioxidant response
Apaf-1 = apoptotic peptidase activating factor 1
Bax = Bcl2-associated X protein
Brn-3a = Pou4f1 (BRN3A) POU domain, class 4, transcription factor 1
Brn-3b = Pou4f2 (BRN3B) POU domain, class 4, transcription factor 2
CNS = central nervous system
HDAC1 = histone deacetylase 1
Htt = Huntingtin
MEFs = mouse embryonic fibroblasts
MELFs = mouse embryonic lung fibroblasts
MPTP = 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine
NGF = nerve growth factor
NOXA = PMAIP1 (phorbol-12-myristate-13-acetate-induced protein 1)
Nrf2 = NFE2L2 (nuclear factor [erythroid-derived 2]-like 2)
ROS = reactive oxygen species

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2. Cristina Lanni, Marco Racchi, Maurizio Memo, Stefano Govoni, Daniela Uberti. 2012. p53 at the crossroads between cancer and neurodegeneration. *Free Radical Biology and Medicine* **52**:9, 1727-1733. [CrossRef]