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Emerging Roles of p53 in Glial Cell Function in Health and Disease

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Abstract

Emerging evidence suggests that p53, a tumor suppressor protein primarily involved in cancer biology, coordinates a wide range of novel functions in the CNS including the mediation of pathways underlying neurodegenerative disease pathogenesis. Moreover, an evolving concept in cell and molecular neuroscience is that glial cells are far more fundamental to disease progression than previously thought, which may occur via a noncell-autonomous mechanism that is heavily dependent on p53 activities. As a crucial hub connecting many intracellular control pathways, including cell-cycle control and apoptosis, p53 is ideally placed to coordinate the cellular response to a range of stresses. Although neurodegenerative diseases each display a distinct and diverse molecular pathology, apoptosis is a widespread hallmark feature and the multimodal capacity of the p53 system to orchestrate apoptosis and glial cell behavior highlights p53 as a potential unifying target for therapeutic intervention in neurodegeneration.

Keywords

p53; glia; neurodegeneration

INTRODUCTION

p53, a tumor suppressor gene encoding a 393-amino acid, 53-kDa protein product, belongs to a family of highly homologous proteins, including p63 and p73, which exist as a large array of isoform variants intricately connected to p53 regulation (Collavin et al., 2010) (Fig. 1). The p53 protein regulates crucial and multifaceted functions in cell-cycle control, apoptosis, and the maintenance of genetic stability (Kruse and Gu, 2009). Subsequently, p53 mutations were identified in half of all human cancers (Hainaut and Hollstein, 2000; Olivier et al., 2004). Consequently, p53 was aptly dubbed “the guardian of the genome” (Lane, 1992) due to its pivotal role in protecting organisms from cellular stresses triggering cancer.

Upon activation, the classical model of p53 regulation involves three sequential steps: (1) stress-induced stabilization, (2) sequence-specific DNA binding, and (3) promoter-specific transcriptional activation (Fig. 2). P53 acts as a crucial node in a network of intracellular control pathways, governing the cellular response to diverse levels of stress with apoptosis, cell cycle arrest, replicative cell senescence, DNA repair, cell metabolism, or autophagy. However, it is apparent that p53 functions with more complexity than originally thought (Kruse and Gu, 2009; Vousden and Prives, 2009). Evidence from disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) poses intriguing questions regarding the function of p53 in different cellular environments (Jacobs et al., 2006). Furthermore, p53 activities in glial cells contribute to various forms of neurodegeneration in a noncell-autonomous fashion. In this review, we discuss recent developments proposing novel roles for p53 in the CNS and examine the evidence linking p53 to various neurodegenerative diseases in different glial cellular contexts.

p53 in Neurons

The primary role of p53 in the context of postmitotic neurons is principally as a regulator of cell survival. Recent studies have elucidated discrete signaling pathways within neurons that control the p53 response to a broad range of cellular insults including excitotoxicity, oxidative stress, and genotoxic stress (Fig. 3). These insults give rise to DNA strand breaks, which then initiate multiple signaling cascades via p53's nuclear transcription and mitochondrial transcription-independent functions (Speidel, 2010; Vaseva and Moll, 2009).

P53 can also direct axonal and neurite outgrowth by regulating the expression of the actin-binding protein Coronin 1b and the small GTPase Rab13, both of which are crucial for cytoskeletal remodeling (Di Giovanni et al., 2006). This function is mediated by acetylated p53, a post-translational modification recently shown to induce a novel transcriptional module involving p53 and the histone acetyltransferases (HATs), CREB-binding protein/p300 (CBP/p300), and p300–CBP-associated factor (P/CAF) to enhance expression of the axonal growth-associated protein 43 (GAP-43) (Gaub et al., 2010; Tedeschi et al., 2009). Conversely, transcription-independent roles for p53 in axonal remodeling have been reported. In primary hippocampal neurons, phosphorylated p53 localizes to the axon to directly interfere with Rho kinase (ROCK), a regulator of both the actin and microtubule system, to promote axonal outgrowth (Qin et al., 2009). Moreover, the secreted axonal growth cone guidance protein semaphorin 3A has been linked to growth cone collapse by truncation of phosphorylated p53, which is dependent on activation of extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), and phosphorylation of the calcium-regulated cysteine protease m-calpain (Qin et al., 2010). In terms of disease, p53, p63 α and p63 γ induce the phosphorylation of tau at the tau-1 epitope in cultured mammalian cells, whilst p73 α induces tau phosphorylation at the tau-1 and PHF-1 antigenic sites (Hooper et al., 2006, 2007, 2010); two epitopes that are highly phosphorylated in Alzheimer's disease patients *in vivo*. The effects of the p53 family on tau phosphorylation are likely to be indirectly mediated as highlighted by the compartmental segregation of tau and p53 family members inside the neurone. Experiments using transcriptionally inactive p53 family members (*N,N*-terminally truncated isoforms of p73

and p63, and p63 isoforms containing point mutations in the DNA binding domain) indicate that tau phosphorylation is driven by a mechanism dependent on gene transcription.

The unique excitable properties of neurons have drawn attention to other examples of p53 pleiotropy. Synaptic NMDA receptor activity in mouse hippocampal neurons can promote neuronal survival by suppressing p53 expression and transcription of p53 pro-apoptotic target genes, coinciding with the induction of nuclear calcium-regulated neuroprotective genes and the inhibition of mitochondrial membrane permeability (Lau and Bading, 2009). Whole-genome expression profiling of NMDA receptor signaling has also revealed an upregulation of Bcl6, a putative p53 transcriptional repressor (Zhang et al., 2007). Furthermore, a recent study demonstrated a link between neuronal p53 and GABA receptor (GABA-R) signaling. In a mouse model of seizure, p53 transcriptionally upregulated brain-expressed RING finger protein (BERP), which, when deleted, decreased both the amplitude of GABA_AR-mediated miniature inhibitory postsynaptic currents (mIPSCs) and surface expression of GABA_ARs, suggesting a role for p53 via BERP in GABAR trafficking (Cheung et al., 2010). With regard to neurodegeneration, research into the molecular mechanisms of AD, PD, and HD is beginning to highlight a key role for p53 in disease pathogenesis (Table 1). Similarly, the apparent deregulation of autophagy in neurodegenerative disease is stimulating interest (Cheung and Ip, 2011), and a role for p53 in mediating autophagic mechanisms upon proteosomal-inhibition-induced neurotoxicity and excitotoxic-induced neurotoxicity has been recently revealed (Du et al., 2009; Wang et al., 2009). Lastly, other emerging roles for neuronal p53 include the regulation of oxidative metabolism (Chatoos et al., 2009; O'Connor et al., 2008), and involvement in a novel lysosomal-driven apoptotic route (Gowran and Campbell, 2008; Fogarty et al., 2010). With such a diverse range of functions, a top-down approach to studying this protein, based on its unique functions in particular cell types, may provide further insights into how best to manipulate p53 for therapeutic gain.

p53-Mediated Neurodegeneration: Emerging Roles for Glia

Table 1 offers a review of the evidence linking p53 to some of the most common neurodegenerative diseases, and indicates that the p53 system is active and contributes to disease progression. However, the exact cellular and molecular mechanisms by which this occurs remain elusive. An emerging theme is that glial cells may act as essential cellular arbitrators in neurological diseases via a noncell-autonomous disease mechanism (Fig. 4). Indeed, much of the early data regarding p53 and neurodegenerative disease were obtained using techniques that, in general, lack cellular resolution, such as PCR, Western blot, and ELISA. Moreover, many of the initial studies linking p53 with nervous system injury and degeneration somewhat overlooked the involvement of glia, and thus arrived at neuron-centered conclusions (Djebaili et al., 2000; Martin and Liu, 2002; Morrison et al., 1996; Napieralski et al., 1999; Qin et al., 1999; Sakhi et al., 1994; Watanabe et al., 1999). As such, the contribution of glial cells in brain tissue and mixed cell cultures is likely to be underestimated. Current theories underlying the processes of noncell-autonomous neurodegeneration include: (i) an intrinsic glial mutant protein expression leading to the disruption of normal glial function and/or changes in glial responses that subsequently

trigger downstream damage to vulnerable neurons; and (ii) neuronal toxicity itself instigating toxic responses from neighboring glia (Lobsiger and Cleveland, 2007).

p53 and Astrocytes

As the most numerous and diverse glial cells in the CNS, astrocytes serve a wide range of functions (Sofroniew and Vinters, 2010). Increasingly, astrocytic p53 is proving fundamental in orchestrating neurodegenerative disease pathogenesis. Astrocyte dysfunction coordinates disease-related mechanisms in HD (Shin et al., 2005), spinocerebellar ataxia (SCA) (Custer et al., 2006), amyotrophic lateral sclerosis (ALS) (Di Giorgio et al., 2007; Nagai et al., 2007), and numerous other neurological disorders (Seifert et al., 2006). Regarding p53, NMDA-mediated CNS excitotoxicity generates a hypertrophic astrocyte morphology associated with changes in p53 expression and nuclear active caspase-3 in the absence of cell death (Villapol et al., 2007). In a prion disease cell culture system, astrocytes exposed to a prion protein fragment (PrP^c) displayed rapid, stress-induced proliferation, and reactivity correlating with increased p53 levels (Hafiz and Brown, 2000). P53-immunoreactive astrocytes are also seen in cortical CNS regions after ischemia (Chung et al., 2002). Furthermore, astrocytes display p53 expression in HIV-associated neurocognitive disorder (HAND) (Jayadev et al., 2007) as do viral-infected astrocytes in models of spongiform encephalomyelopathy (Kim et al., 2002), suggesting viral infections may promote a common route of p53 accumulation in astrocytes. In addition, p53 is implicated in oxidative stress-mediated astrocyte cell death after stimulation by the intercellular messenger nitric oxide (NO) (Yung et al., 2004) and by direct, transcription-independent signaling to the mitochondria (Bonini et al., 2004). Ammonia-induced astrocyte swelling, a phenomenon underlying cytotoxic brain edema associated with acute liver failure, activates p53 and this astrocytic swelling is suppressed by the p53 inhibitor pifithrin- α (PFT- α) (Panickar et al., 2009). Such behavior may be related to the process of reactive astrogliosis. Recently, an intriguing relationship between p53 and tunneling-nanotubes (TNTs) has transpired. TNTs are thin membranous extensions that form channels between cells for intercellular communication and trafficking and are found in numerous cell types, including neurons and astrocytes; ongoing research to uncover their functional significance is still in its infancy (Davis and Sowinski, 2008). In cultured hippocampal astrocytes, p53 appears critical for TNT development via epidermal growth factor receptor (EGFR) activation and a downstream pathway involving AKT8 virus oncogene cellular homolog (Akt), phosphoinositide 3-kinase (PI3K), and mammalian target of rapamycin (mTOR). Moreover, TNTs can transfer intraand extracellular amyloid beta (A β) between astrocytes and neurons (Wang et al., 2011). TNTs can mediate the intercellular transfer of prion protein (PrP^{Sc}) between neurons, and between dendritic cells and neurons (Gousset et al., 2009), and neuropathological changes in AD, PD, and HD have recently been hypothesized to spread in a “prion-like” manner (Brundin et al., 2010). Thus, this aspect of p53’s function may be an attractive target for minimizing the propagation of toxic protein aggregates seen in neurodegenerative diseases.

p53 and Oligodendrocytes

The essential function of oligodendrocytes is the formation of myelin sheaths, which serve to insulate neuronal axons and facilitate the fast salutatory conduction of action potentials in the CNS, as well as the peripheral nervous system (PNS) by their myelinating Schwann cell counterparts (Bradl and Lassmann, 2010). The death of oligodendrocytes and/or damage to their myelin sheaths is seen in demyelinating diseases such as multiple sclerosis (MS) and vanishing white matter disease (VWM) (Franklin and Ffrench-Constant, 2008; van der Knaap et al., 2006), and has also recently been linked to AD (Desai et al., 2011). MS is a chronic inflammatory demyelinating disease marked by oligodendrocytes loss and axonal degeneration (McQualter and Bernard, 2007). The exact trigger and primary cause of MS remains unclear and there is considerable debate over what drives the primary pathology; the neurodegenerative component, or the inflammatory-mediated element (Trapp and Nave, 2008). Oligodendrocyte p53 may be involved in disease pathogenesis of MS and in the animal MS model, experimental autoimmune encephalomyelitis (EAE). Thus, when primary postmitotic human oligodendrocyte cultures are treated with tumor necrosis factor- α (TNF α), a proinflammatory cytokine commonly present at injury sites in numerous neurodegenerative diseases (McCoy and Tansey, 2008), p53 is persistently induced and contributes to human oligodendrocyte apoptosis (Ladiwala et al., 1999). Moreover, a combination of *in situ* analysis of MS tissue with *in vitro* functional assays of adult human oligodendrocytes revealed that p53 primes oligodendrocytes for apoptosis by upregulating the Fas death receptor (FasR) and death receptors 4 (DR4) and 5 (DR5), to culminate in cell death by their associated ligands (Wosik et al., 2003). Conversely, p53-deficient EAE mice display more extensive demyelination and a more severe disease course than wild-type controls, implying a regulatory role for p53 in suppressing the inflammatory reaction toward oligodendrocytes in the CNS (Okuda et al., 2003). Interestingly, in a recent study using the cuprizone model of demyelination, p53 inhibition reduced microglial activation and myelin loss in the corpus callosum of mice, and enhanced repair by resident oligodendrocyte progenitors and multipotent stem cells of the subventricular zone (SVZ) (Li et al., 2008). As both p53 and p73 can mediate normal oligodendrocyte development (Billon et al., 2004), whether this role affects OPC recruitment and remyelination of axons in demyelinating diseases such as MS deserves investigation. P53 has also been shown to be activated in oligodendrocytes in HIV associated neurocognitive disorder (HAND) (Jayadev et al., 2007).

P53 and Microglia

Microglia are the resident immunocompetent cells of the CNS and exist in the normal CNS in a surveillance state, characterized by a small cell body, extensively branched fine processes and downregulated expression of many proteins and receptors (Nimmerjahn et al., 2005; Raivich, 2005). This behavior is thought to be mediated by intercellular messengers and neurotransmitter signaling between microglia and neurons (Biber et al., 2007; Pocock and Kettenmann, 2007). During neurological insults, microglia undergo dramatic changes in their morphology and proceed to an “activated” phenotype defined by a hypertrophic cell body and fewer, retracted processes (Garden and Moller, 2006). Once activated, microglia may release various proinflammatory factors, such as TNF α , interleukin-1 β (IL-1 β), NO, and superoxide (SO) (Block et al., 2007), which can kill both neurons and microglia.

Activated microglia are increasingly implicated as key contributors in the progression of numerous neurodegenerative diseases (Block et al., 2007; Davenport et al., 2010; Glass et al., 2010; Hooper et al., 2009a,b; Streit, 2005).

Microglia, p53, and AD

Microglia become activated and congregate around A β plaques in AD (El Khoury and Luster, 2008; McGeer and McGeer, 2010) and imaging of patients with mild AD shows microglial activation in the entorhinal, temporoparietal, and posterior cingulate cortex indicating an early inflammatory response (Cagnin et al., 2001; Huang et al., 2002). Moreover, evidence suggests a strong correlation between extensive microglial activation and increasing cognitive decline in AD patients (Blasko et al., 2004; Edison et al., 2008). Experiments with AD transgenic mice confirm early microglial reactivity before obvious plaque formation as well as microglial activation by extracellular A β accumulation (Rodriguez et al., 2010). This suggests that further factors may influence the activation of microglia in AD, particularly at early stages. A high incidence of microglial apoptosis has also been observed in AD brains (Lassmann et al., 1995), and analysis of postmortem AD brain revealed high levels of p53 in glial cells as well as wide-spread glial cell apoptosis (de la Monte et al., 1997; Kitamura et al., 1997). Furthermore, microglial responses to A β peptides result in severely compromised neuronal viability (Qin et al., 2002; Sondag et al., 2009). Recently, Davenport et al. (2010) demonstrated that p53 expression is increased in microglia exposed to A β_{25-35} peptides, and triggered neuronal apoptosis when neurons were exposed to microglial-conditioned culture medium. Importantly, microglial apoptosis and microglial-induced neurotoxicity was decreased when microglia were treated with the p53 inhibitor pifithrin- α (PFT α), suggesting that targeting microglial p53 pathways in AD may have neuroprotective effects by reducing the production of microglial-derived neurotoxins (Davenport et al., 2010). Whilst further research is needed to consolidate the evidence for p53's role in sculpting microglial behavior, proapoptotic proteins may control microglial activation without triggering microglial death. Thus, the function of p53 and its family members in microglia may be more diverse than their functions in other cell types.

Microglia, p53, and HIV-associated neurocognitive disorders

HAND develops in a subset of HIV infected individuals. The HIV virus enters the CNS and establishes persistent infection in cells of myeloid origin (microglia and perivascular macrophages). Thus, the neurological dysfunction as well as the neuronal and synaptic loss observed in these patients may occur in response to chronic neuroinflammation initiated by infected CNS myeloid cells. Subsequently, accumulation of p53 protein was observed in CNS tissue from HAND patients (Silva et al., 2003). Multiple cell types, including neurons, astrocytes, microglia, and oligodendrocytes show evidence of p53 activation as well as induction of p53 target gene expression (Garden et al., 2004; Jayadev et al., 2007; Silva et al., 2003). These findings suggest that p53 may modulate the function of several different cell types in HAND, potentially acting to promote apoptotic transcriptional programs in some cell types while facilitating DNA repair or cell cycle arrest in others. Furthermore, considerable experimental evidence supports the hypothesis that p53 participates in HIV mediated neural injury. Simian immunodeficiency virus encephalitis (SIVE), a primate

model of HAND also demonstrated increased nuclear p53 immunoreactivity (Jordan-Sciutto et al., 2000). *In vitro*, neurotoxic HIV-viral protein R (Vpr) triggers apoptosis involving p53 induction (Jones et al., 2007) and cultured neurons show p53 activation when treated with supernatant from monocytoid cells expressing neurotoxic HIV protein Tat (Silva et al., 2003). Exposing neural cultures to HIV-gp120 coat protein induces robust p53 activation and co-culture studies of cells from p53 knockout mice demonstrate that both neurons and microglia must express p53 for gp120-induced neurotoxicity (Garden et al., 2004). While p53 activity in neurons may promote activation of apoptotic cascades, the role of p53 in microglia appears more nuanced, promoting proinflammatory behaviors and suppressing microglia functions that might provide neurotrophic effects (Jayadev et al., 2011; Mukerjee et al., 2010). Exposing cultured astrocytes to Vpr leads to p53 activation and induction of downstream apoptotic pathways mediated by caspase-6 (Noorbakhsh et al., 2010). The importance of this pathway was confirmed in a mouse model of HAND induced by microglia expression of HIV-Vpr, as these mice demonstrated both astrocyte apoptosis and behavioral deficits (Noorbakhsh et al., 2010). Taken together, these data suggest that the inflammatory CNS environment in HAND cause p53 activation in most CNS cell types and p53 function in turn may exacerbate the proinflammatory response as well as subsequent neurodegeneration.

Concluding Remarks

Clearly p53 functions in the nervous system are more complex than the classical pathways of p53 activation and regulation of cell-cycle control and cancer prevention. Indeed, the recent hypothesis that cancer and neurodegeneration might share mechanistic foundations (Morris et al., 2010; Plun-Favreau et al., 2010) lends credence to suggestions that the same protein can behave in drastically different ways in divergent cell types. At the same time, the role of p53 in brain gliomas including astrocytomas, oligodendrogliomas, and oligoastrocytomas must be heeded when considering the therapeutic potential of p53 regulation in neurodegeneration (Hede et al., 2001; Lo et al., 2011). Thus inflammation and enhanced macrophage-derived TNF α production may promote resistance to p53-mediated apoptosis and serve as independent negative prognostic factors for a range of cancers (Lo et al., 2011). Given the critical nature of p53 to the survival of every cell type in the body it seems logical that a significant degree of functional plasticity is required for this protein to adapt to the cellular context in which it is placed. As such, a deeper understanding of p53 in the context of health and disease is urgently needed. Though differing genetic and environmental factors might initially trigger the molecular and cellular pathology found in neurodegenerative diseases, including AD, PD, and HD, the mounting evidence for p53's crucial role in disease progression cannot be ignored. Indeed, it is interesting to note that p53 is the crucial link between the telomere and mitochondrial theories of ageing (Sahin et al., 2011), which is itself the greatest risk factor for many neurodegenerative diseases (Bishop et al., 2010). The emerging role of glial cells in disease exemplifies the multifarious behavior of p53 in different cellular environments with each main class of glial cell commanding a variety of complex interactions with neurons, making glia core mediators of neuronal survival in many disease states. This noncell-autonomous pathophysiology appears to be heavily dependent on p53 functions, in which glial cell p53-dependent signals can

orchestrate distinct phenotypic responses, especially in the case of microglia. In closing, future research into the molecular mechanisms of p53 activities in the CNS in health and disease, as well as a deeper understanding of the specific cell types and intracellular networks involved is irrefutably justified.

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Abbreviations

Aβ	amyloid beta
AD	Alzheimer's disease
Akt	AKT8 virus oncogene cellular homologue
ALS	amyotrophic lateral sclerosis
Aparf-1	apoptotic protease activating factor 1
Arf-BP1	alternative reading frame BP1
ATM	ataxia telangiectasia mutated
BERP	brain-expressed RING finger protein
CBP/p300	CREB-binding protein/p300
Cdk (4/6)	cyclin-dependent kinase
ChK2	checkpoint homologue 2
COP1	mammalian constitutive photomorphogenic 1
DR4	death receptor 4
DR5	death receptor 5
EAA s	excitatory amino acids
EGFR	epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
FasR	fas death receptor
GABA-R	gamma-aminobutyric acid receptor
GAP-43	growth-associated protein 43
HAND	HIV-associated neurocognitive disorder
HATs	histone acetyltransferases
HD	Huntington's disease
IL-1β	interleukin 1 β
JNK	c-Jun N-terminal kinase

MAPK	p38 mitogen-activated protein kinase
mIPSCs	inhibitory postsynaptic currents
MnSOD	manganese superoxide dismutase
mTOR	mammalian target of rapamycin
Myc	avian myelocytomatosis virus oncogene cellular homolog
MS	multiple sclerosis
NF-κB	nuclear factor kappaB
NMDA	<i>N</i> -methyl-D-aspartate
NO	nitric oxide
p14ARF	p14 alternative reading frame protein
PARP-1	poly ADP-ribose polymerase 1
P/CAF	p300-CBP-associated factor
PD	Parkinson's disease
PFT-α	pifithrin-alpha
PI3K	phosphoinositide 3-kinase
Pirh2	p53-induced ring-H2
pRb	retinoblastoma protein
PrPSc	prion protein
Puma	p53 upregulated modulator of apoptosis
Ras	rat sarcoma
ROCK	Rho kinase
ROS	reactive oxygen species
SCA	spinocerebellar ataxia
SVZ	subventricular zone
SIVE	simian immunodeficiency virus
TNFα	tumor necrosis factor alpha
TNTs	tunneling-nanotubes
VWM	vanishing white matter disease
XIAP	x-linked inhibitor of apoptosis

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Fig. 1.

The p53 family and their major isoforms, including the main sites of posttranslational modifications: Phosphorylation (Phos.), Acetylation (Acety.), ADP-ribosylation (ADP-r.), Ubiquitination (Ubiq.), Glycosylation (Glyco.), Methylation (Methy.), Neddylation (Neddy.), SUMOylation (SUMO.). TA (transactivation) domain, PR (proline-rich) domain, DBD (DNA-binding domain), OD (oligomerization domain), CTD (C-terminal domain), SAM (sterile- α motif) domain.

Fig. 2.

Classical model of p53 activation. Upstream signaling by a variety of DNA damaging agents, growth factor signals, and cellular stresses can trigger p53 activation by three major pathways: (1) DNA damage activates p53 through the protein kinases ATM and Chk2 (Carr, 2000); (2) p53 is activated by aberrant growth signals and cell cycle re-entry, triggered by expression of *Ras* or *Myc*, which in humans is dependent on p14^{ARF} (Sherr and Weber, 2000); (3) cellular stresses, including chemotherapeutic drugs and ultraviolet light, activate p53 independently of ATM, Chk2, or P14^{ARF} (Vogelstein et al., 2000), causing kinase-stabilization of p53 by phosphorylation, leading to dissociation from its principle negative regulator, the E3 ligase protein MDM2, which normally tags p53 for ubiquitin-dependent proteosomal degradation. Other recently identified E3 ligases with similar functions to MDM2 include Pirh2 (Leng et al., 2003), COP1 (Dornan et al., 2004), and Arf-BP1 (Chen et al., 2005). Once stabilized, p53 performs sequence-specific DNA binding and promoter-specific transcriptional activation to ultimately induce the expression of genes involved in either cell cycle arrest and DNA repair or apoptosis.

Fig. 3. p53 signaling in neurons. Upon DNA damage, induced by excitotoxicity, oxidative stress, and/or genotoxic stress, downstream signaling proteins such as PARP-1, ATM/Chk2, Cdk4/6-pRb-E2F1, and JNK stabilize p53 by post-translational modifications including phosphorylation (P) and ADP-ribosylation (ADP), and by p38 blocking interaction with the p53 negative regulator MDM2. Once stable, p53 promotes apoptosis by interacting with members of the pro and antiapoptotic Bcl-2 family proteins at the mitochondria, and promoting expression of proapoptotic proteins Puma, Noxa, Apaf-1, Siva as well as the repression of the anti-apoptotic protein XIAP. Conversely, the transcription factor NF-κB can promote survival signaling pathways via competition with p53 for the co-transcription factor p300 and the subsequent expression of antiapoptotic proteins Bcl-2, XIAP, and Mn-SOD. Additionally, newly identified physiological roles for neuronal P53 that are not directly related to stress include several pre and postsynaptic functions.

Fig. 4.

p53 in glia. P53 mediates HAND. HIV infection leads to p53 activation in several CNS cell types. HIV infects perivascular macrophages and microglia which can release viral proteins including Tat, gp120, and Vpr that act on microglia to promote a proinflammatory response and microglial activation, which is dependent of p53, and triggers the release of neurotoxic molecules such as TNF- α , IL-1 β , NO, and ROS that are toxic to microglia, astrocytes, oligodendrocytes, and neurons. Viral proteins also act on astrocytes, leading to astrocyte dysfunction which could potentiate the excitotoxic response in neurons and oligodendrocytes by release of proinflammatory molecules including ROS and EAAs. HIV proteins, ROS, and excitotoxic levels of EAAs can all promote p53 stabilization in the nucleus, supporting a proinflammatory response in microglia and expression of proapoptotic p53 target genes that promote astrocyte and neuron apoptosis. In astrocytes, p53 is also involved in the development of TNTs, which are hijacked by A β and toxic prion proteins and may contribute to the spread of toxic protein aggregates in neurodegeneration. In oligodendrocytes, p53 has also been linked to myelination as p53 inhibition promotes remyelination (see main text).

TABLE 1

Routes and Roles of p53 Activity in Neurons in Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's Disease (HD)

Disease	Experimental model	Findings	Reference
AD	Human neuroblastoma	Intracellular A β ₁₋₄₂ displayed direct transcriptional control of the p53 promoter	Ohyagi et al., 2005
	HEK cells	P53 phosphorylates the microtubule-associated protein (MAP) tau	Hooper et al., 2007
	Human and mouse brain tissue, HEK cells	P53 is transcriptionally regulated by the APP intracellular domain (AICD) and can also upregulate <i>Pen2</i> expression by a presenilin 1 (PS1) and PS2-dependent mechanism	Alves da Costa et al., 2006b, Dunys et al., 2009
	TSM-1 cells, mouse fibroblasts, HEK cells	Components of the Y-secretase complex, namely Aph-1a, Aph-1b, Pen-2, and nicastrin, can modulate neuronal cell death in a p53-dependent fashion	Checler et al., 2010; Dunys et al., 2007
	Primary neurons (rat), SH-SY5Y cells	P53 acts as molecular link between double-stranded RNA-dependent-protein kinase (PKR) and mammalian target of rapamycin (mTOR) in A β ₄₂ -induced neurotoxicity	Morel et al., 2009
	SY5Y cells	Secretase inhibitors prevent p53 upregulation and decrease intracellular A β levels	Ma et al., 2009
	Mouse N2a β , SH-SY5Y, primary neurons (rat)	Activation of endogenous p53 decreases intracellular levels of amyloid precursor protein (APP)	Cuesta et al., 2009
	Primary neurons (rat)	A β induces p53-mediated lysosomal destabilization and concomitant increase in cytosolic cathepsin-L activity	Fogarty et al., 2010
PD	PC12 and SH-SY5Y cells	Dopaminergic toxin 6-hydroxydopamine (6-OHDA) increases p53 and its pro-apoptotic targets BIM and PUMA	Biswas et al., 2005; Gomez-Lazaro et al., 2008
	Mouse embryonic dopaminergic neurons	6-OHDA activates p53 via ATM kinase phosphorylation	Nair, 2006
	TSM-1 cells, SH-SY5Y cells	6-OHDA eradicates the p53-dependent neuroprotective properties of wild-type α -synuclein	Alves da Costa et al., 2006a
	Rat forebrain, nigral dopaminergic neurons	6-OHDA induces oxidative damage and apoptosis via NF- κ B and p53 activation	Liang et al., 2007
	Zebrafish dopaminergic neurons	<i>DJ-1</i> and <i>mdm2</i> knockdown triggers neuronal cell loss. P53 inhibition rescues neuronal loss after exposure to hydrogen peroxide and proteasomal inhibition	Bretaud et al., 2007
	P53-deficient mice	P53 mediates <i>Bax</i> transcriptional induction upon mitochondrial complex 1 inhibition	Perier et al., 2007
	SH-SY5Y cells	Monoamine oxidase-B (MAO-B) inhibitor prevents 1-methyl-4-phenylpyridinium (MPP)-induced p53 transactivation and cell death	Sanz et al., 2008
	N2a, HEK, H1299 cells	DJ-1 interacts with p53 and provides neuroprotection via inhibition of the p53-Bax-caspase pathway	Fan et al., 2008
HD	Human/mouse brain tissue, P53-deficient fibroblast, TSM1, HEK, SH-SY5Y cells	<i>Parkin</i> acts as p53 transcriptional repressor by interacting with the p53 promoter. Autosomal recessive juvenile PD mutations subsequently shown to abolish this role.	da Costa et al., 2009
	HEK cells	Mutant <i>huntingtin</i> (<i>Htt</i>), containing a polyglutamine repeat, co-aggregates with p53 and represses transcription of the p53-activated promoter <i>p21^{waf-1/cip1}</i> in biochemical assays	Steffan et al., 2000
	Cloned embryonic striatal neurons (rat)	Gene expression profiles upon transfection with different N-terminal fragments of mutant <i>Htt</i> show an increased expression of many genes regulated by p53	Sipione et al., 2002
	P53-deficient embryonic cortical neurons (mouse), PC12 cells, HD patient lymphoblasts, mutant <i>Htt</i> Drosophila, mutant <i>Htt</i> transgenic mice	Mutant <i>Htt</i> binds p53 and increases its transcriptional activity. Mitochondrial membrane depolarization and cytotoxicity prevented after treatment with PFT- α , RNA interference, or genetic deletion of p53	Bae et al., 2005

Disease	Experimental model	Findings	Reference
	H1299, HCT116, Vm10 cells, p53-deficient mice	Human <i>Htt</i> gene contains three potential p53-responsive elements not found in the pathogenic domain of mutant <i>Htt</i> . P53 increased <i>Htt</i> gene expression after DNA-damage	Feng et al., 2006
	Primary striatal neurons (rat), mutant <i>Htt</i> knock-in embryos (mouse), HEK and SH-SY5Y cells	Loss of phosphorylation of mutant and wild-type Htt mediates neurotoxicity in p53-dependent manner	Anne et al., 2007
	Rat Intrastratial infusion, striatal tissue (rat)	Administration of HD model mitochondrial toxin triggers p53-mediated autophagic and apoptotic cell death	Zhang et al., 2009