Review

Neurodegenerative Diseases

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Role of p53 in Neurodegenerative Diseases

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p53 · Neurodegenerative disease · HIV-associated neurocognitive disorders

Abstract
Background: p53 plays an important role in many areas of cellular physiology and biology, ranging from cellular development and differentiation to cell cycle arrest and apoptosis. Many of its functions are attributed to its role in assuring proper cellular division. However, since the establishment of its role in cell cycle arrest, damage repair, and apoptosis (thus also establishing its importance in cancer development), numerous reports have demonstrated additional functions of p53 in various cells. In particular, p53 appears to have important functions as it relates to neurodegeneration and synaptic plasticity. ***Objective:*** In this review, we will address p53 functions as it relates to various neurodegenerative diseases, mainly its implications in the development of HIV-associated neurocognitive disorders. ***Conclusion:*** p53 plays a pivotal role in the development of neurodegenerative diseases through its interaction with cellular factors, viral factors, and/or small RNAs that have the ability to promote the development of these diseases. Hence, inhibition of p53 may present an ideal target to restore neuronal functions.

Introduction

Known as a 'guardian of the genome', p53 protein plays a crucial role in coordinating cellular responses to genotoxic stress [1, 2]. p53 mediates tumor suppression by a variety of mechanisms, including cell cycle arrest, apoptosis, and cellular senescence [3]. p53 expression and activity are tightly regulated, such that p53 protein product is either rapidly degraded or exists in a latent form in unstressed cells. However, the steady-state levels and transcriptional activity of p53 increase dramatically in cells that sustain various types of stress. Due to its great importance in cellular functions, the expression of p53 is regulated at multiple levels, including transcriptional, post-transcriptional, pre-translational, and post-translational [4]. Further, both p53 activation and regulation involve complex posttranslational modifications. Upon proper translational modifications, p53 activity includes signal transduction, transcriptional activation, and transcriptional regulation. Its role in transcriptional activation is especially intriguing in that p53 induces proapoptotic gene expressions, both in the mitochondria as well as the nucleus. A growing number of studies are demonstrating the importance of mitochondrial integrity and function in neurodegenerative diseases [5–8].

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Generally, p53 constitutively expression is kept at low levels through proteasomal degradation. To date, MDM2 (murine double minute 2)-mediated poly-ubiquitination and degradation of p53 protein has best been characterized, although several other E3 ubiquitin ligases – such as MDMX, Pirh2 (p53-induced RING-H2 domain protein), and COP1 (constitutively photomorphogenic 1) – also induce p53 degradation [9]. Additionally, an F-box protein, JFK (Just one F-box and Kelch domain-containing protein), targets p53 for degradation through the SCF (Skp, Cullin, F-box containing complex)-dependent pathway [10]. Interestingly, Skp2 (S-phase kinase-associated protein 2), another F-box protein that interacts with the SCF complex, targets p300, thereby inhibiting p53 acetylation [11] and transcriptional activity [12]. Overall, in the absence of any cellular damage, p53 activity is tightly controlled through many different mechanisms. Further, the continued expression and degradation of p53 assures its role as a surveillance factor for detecting/transducing cellular stress or injury.

Upon encountering cellular damage, p53 becomes stabilized through various pathways. For example, recent studies have shown that p53 is deubiquitinated by USP10 (ubiquitin specific peptidase 10), thereby rescuing p53 from proteasomal degradation [13]. Also, when DNA is damaged, ATM (ataxia telangiectasia mutated) phosphorylates MDM2 [14]. Such phosphorylation is thought to inhibit MDM2 interaction with p53 as well as inhibiting MDM2 oligomerization [15]. ATM also phosphorylates p53 at ser15, thereby further stabilizing and activating p53 [16]. Subsequent nuclear translocation of p53 leads to transcriptional enhancement of numerous genes, including p53 itself. Therefore, release of p53 from the proteasomal degradation pathway further enhances its own expression. In contrast to E3 ligases, p53 stability/activity is positively affected by transducers/responders of cellular injury, and it is this activation that may affect the role of p53 in neurons.

Functional Role in Neurons

One likely paradigm that explains neuronal deregulation consists of continued low-grade neuronal stress/injury, such as oxidative stress [17, 18], that leads to mitochondrial dysfunction [19–23]. Continued mitochondrial dysfunction would, in turn, affect numerous cellular processes – such as axonal transport, synaptic plasticity, and membrane potential – and eventually lead to death [24–26]. Regardless, the key events (mitochondrial dysfunction and apoptosis) in neuronal deficit appear to be mediated by p53, as shown in the following sections.

In neurodegenerative diseases, like HIV-associated neurocognitive disorders (HAND), Alzheimer's disease (AD), Parkinson disease (PD), and ischemic stroke, the manifestation of clinical symptoms results from the process of gradual neural degeneration and ultimately death of a specific population of neurons. In many types of post-mitotic neurons, p53 may mediate apoptosis resulting from many types of insults, including DNA damage, hypoxia, starvation (withdrawal of trophic support), hypoglycemia, oxidative stress, and viral infection [27]. Recently, many studies on neurodegenerative disease have suggested that p53 is a player in neuropathogenesis, and have reported neuronal cell death associated with enhanced levels of p53 [28–30]. Dopaminergic neurons of the substantia nigra pars compacta are mostly affected in PD, and dopaminergic death may involve oxidative stress, inducing in turn DNA damage and p53 activation [31]. Evidence of DNA fragmentation and chromatin condensation in melanized cells of the substantia nigra of PD patients compared to controls favors the involvement of apoptosis in the neuropathogenesis of PD [32, 33]. Increased levels of the p53-dependent proteins Bax (Bcl-2 associated X protein) and caspase-3 have also been reported in the PD nigral dopaminergic neurons [22]. The aggregation of neurotoxic amyloid protein in the brain is believed to be the cause of AD and associated neuronal death linked to oxidative stress [34]. The increase in the level of p53 has been detected in the brain tissue of AD patients [35] and in the brain of transgenic mice overexpressing amyloid β1–42 [36].

Posttranslational modification of p53 plays a prominent role in its activity in that, whereas poly-ubiquination leads to proteasomal degradation, acetylation seems to be required for some of its functions. In fact, p53 can be modified by poly- and mono-ubiquination, acetylation, sumoylation, phosphorylation, glycosylation, methylation and neddylation [37]. Undoubtedly, different combinations of posttranslational modifications would have differing affects on p53 function. As such, in neurons, Lee et al. [38] showed that phosphorylation of serine residues located at positions 15, 33, and 36 within p53 leads to transcriptional induction of genes involved in apoptosis.

Interestingly, in numerous neurodegenerative diseases, p53 activation often corresponds with the induction of the apoptotic machinery, including the induction of both mitochondrial and nuclear gene expressions. However, an additional function for p53 in neurons is illustrated by recent studies demonstrating p53 playing a sig-

nificant role in neuronal maturation and function. It appears that the key event in determining whether p53 transcriptionally induce the apoptotic pathway or neurite extension is governed by its acetylation. Namely, Gaub et al. [39] showed that the acetylation of p53 by CBP (CREB-binding protein)/p300 allows transcriptional induction of genes required for neurite outgrowth. Interestingly, previous studies showed p53 acetylation at Lys320 leads to neurite outgrowth and axonal regeneration while Lys373 acetylation leads to apoptosis [40, 41]. The group also demonstrated P/CAF (P300/CBP-associated factor) as the functional enzyme in acetylating p53 at Lys320. Upon acetylating p53 at Lys320, they found upregulation of Corona1, Rab13 (Ras-related protein), and Gap43 (growth associated protein 43), all of which are genes thought to be important for neurite outgrowth. Tedeschi et al. [42] also showed that p53-induced cGMP-dependent protein kinase type I (cGKI) expression overcomes growth cone collapse and retraction mediated by Sema3A. Others attribute p53 to mediating NGF-mediated amplification of Wnt signaling that also leads to neurite outgrowth [43], and may further explain how NGF functions as a survival factor for neurons. Together, these findings show the importance of p53 in neurite outgrowth and maintenance. Considering the pro-survival (neuronal maturation and axonal maintenance) versus the apoptotic functions of p53, it is intriguing to speculate on the possible mechanism(s) of how neurons mobilize p53 upon injury or stress caused by intrinsic and extrinsic factors.

Away from cell death, p53 deregulation can have possible sub-lethal effects on neurons, such as synaptic plasticity and neuronal communications [44]. This p53 function is common to most neurodegenerative diseases. To our knowledge, besides cell death and neuronal communication, no other common pathogenic theme/hallmark among these diseases (HIV-1, AD, HD, PD) can be accounted for by p53 (fig. 1).

In the following sections, we will discuss involvement of p53 in several degenerative diseases with a focus upon its role in the development of HAND.

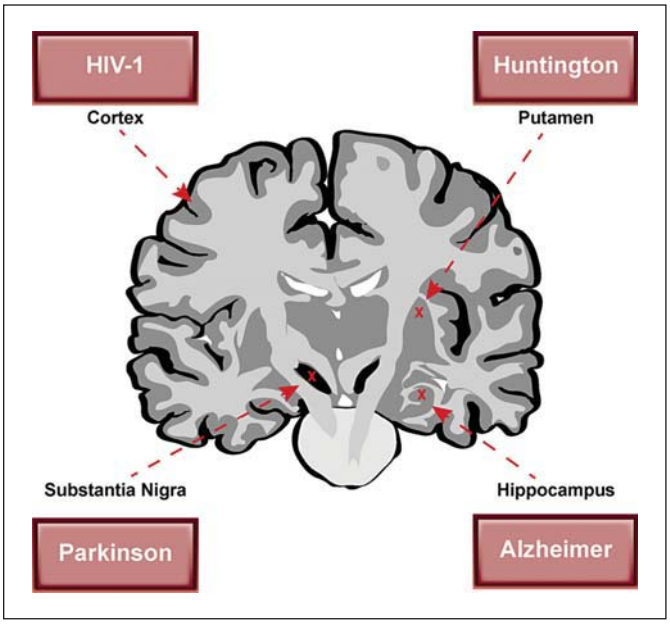

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Fig. 1. Brain areas affected by neurodegenerative diseases. Schematic representation (coronal section through caudal parts of the ventral lateral nucleus, massa intermedia, and basilar pons) of the brain areas that are initially damaged by various neurodegenerative diseases. The names of the affected areas are marked (X).

Role of p53 in HAND Development

Prior to the introduction of highly active antiretroviral therapy (HAART), 30% of the HIV-1 infected patients in the United States rapidly developed HAND accompanied by tremendous neuronal deficit [45–47]. HAND are characterized by cognitive decline, behavioral changes, and motor dysfunction [48]. As reflected in the clinical symptoms, the neurodegeneration is prominent in the basal ganglia, though other regions of the CNS are also affected [49]. The neuropathology is further characterized by HIV-1 encephalitis with a variable degree of perivascular inflammation [50]. The cellular and molecular mechanisms leading to the development of HAND remain unclear. However, several reports point to the involvement of cellular (cytokines, chemokines) and viral (Tat, gp120, Vpr, Nef) proteins in this phenomenon. In addition, numerous reports have described that neuronal deregulation and HAND development are p53-dependent [26, 51–54], most likely due to the increased transcription of proapoptotic genes both in the nucleus and the mitochondria [23] along with p53-mediated inhibition of pro-survival gene expression [24].

However, considering that the prevalence of HAND continues to increase, even during the HAART era, it appears that neuronal deregulation increases and neuronal loss no longer plays a major role in HAND development.

Although not within the focus of this review, compelling neuropathological data have described that the HAND disease process occurs with an ongoing virus presence, and that despite therapy HAND remain very

prevalent [55]. In addition, several of the minor cognitive motor disorder cases have latent infection – given the success of the therapy, it is probable such cases remain because there are more latent cases [55–57]. On the other hand, in a recent study, Dr. K. Collins's team described that HIV-1 infects multipotent hematopoietic stem and progenitor cells. These cells allow the virus to hide and to be reactivated and re-infect additional cells, even in the HAART era [58]. The presence of latent HIV-1 reservoirs in CD4+ T cells and in the monocyte-macrophage lineage can clarify the persistence of HIV-1 and the prevalence of HAND [59–65]. It is not clear what the role of p53 is or how it contributes to this phenomenon.

Concerning less neuronal loss, one possible explanation was described by Garden et al. [52] where they demonstrated that wild-type p53 is required both in HIV-1-infected microglia to produce neurotoxic factors (including viral proteins) as well as in neurons for mediating neurodegeneration. Further, p53 was shown to be upregulated in the brain tissues of HIV-infected patients with neurological disorders. For example, DNA damage, which is one of the main activators of p53, has been detected in the brains of HAND patients [66], and an increase in the expression of both p53 and growth hormone receptor was observed in brain tissue from HIV-infected patients compared with controls. Furthermore, immunohistochemical studies have shown an accumulation of p53 in the nuclei of neurons within the cerebral cortex of HAND patients; the number of neurons with detectable levels of nuclear p53 was higher in AIDS patients with HAND than in the cases without HAND or HIV-negative subjects [52]. The same study revealed an accumulation of p53 in the nuclei of cortical astrocytes and microglia from HAND patients. Western blotting of cortical tissue lysates confirmed the increase in p53 levels in HIV-infected patients with neurological disorders [67]. In addition, cortical neurons lacking p53 are resistant to death mediated by HIV-1 proteins [68].

Examination of brain tissues from HIV-infected patients shows that p53-dependent proteins, such as Bax, are upregulated in microglia and macrophages in the cerebral cortex and basal ganglia of HIV-infected patients with encephalitis when compared to patients without encephalitis and/or HIV-negative subjects [69]. Although all the cells in the CNS express receptors or co-receptors of HIV-1 and can theoretically be infected, HIV-1 mainly productively infects perivascular macrophages and resident microglia with the formation and release of viral particles and ultimately the death of infected cells [70]. The restricted infection of astrocytes has also been reported. This type of infection may result in viral latency and the release of a small number of viruses upon simulation by cytokines [71]. Even though traces of HIV-1 DNA and RNA have been detected in neurons, there is little evidence of productive infection in neurons [72–74]. The absence of considerable neuronal infection suggests that the neurodegeneration results from injuries caused by the indirect effect of HIV-1 infection in the CNS. HIV-1-infected cells in the CNS release HIV-1-associated neurotoxic proteins, such as gp120, Tat, Nef, and Vpr, which participate in the HAND development [75–80].

In support of this observation, p53 was shown to functionally and physically interact with several HIV-1 viral proteins for the benefit of the virus. For example, p53 interaction with HIV-1 reverse transcriptase provides the viral protein with 3′ to 5′ proof reading function during viral replication [81, 82]. Our lab showed that Vpr interacts with p53 to modulate viral gene transcription [83, 84]. We also demonstrated that Tat interacts with p53, which in turn interacts with cdk9 (which forms the p-TEFb, positive transcription elongation factor b, complex with cyclin T1) to phosphorylate the C-terminal domain of RNA polymerase II, thereby facilitating viral transcription [85]. In support of p53's role in HIV replication, Pauls et al. [86] showed that silencing p53 inhibits HIV-1 replication. Furthermore, inhibition of cdk9 with 9-aminoacridine also inhibits HIV-1 replication [87]. All these data point to the involvement of p53 in HIV-1 gene expression and replication, a phenomenon that may lead to the development of HAND.

In this regard, activation of p53 in the neuropathogenesis of HAND might be caused by direct consequences of HIV infection of the CNS and viral proteins like Env (gp120), Tat, Vpr, and Nef influencing the activity of p53 while contributing to the process of neurodegeneration [68, 88–90]. As displayed in figure 2, p53 can be activated by viral proteins following several distinct pathways. In addition to these identified and published pathways, we recently found that gp120, Tat, and Vpr proteins trigger activation of p53 through upregulation of miR-34a in neurons [unpubl. data]. Our data corroborate with published results regarding the relation between upregulation of miR-34a and p53 activation [91–93].

It is noteworthy that the neuropathic hallmark of HIV-1 encephalitis is the formation of multinucleated giant cells, or syncytia, formed by the fusion of HIV-1-infected and non-infected cells in the brain, which involves macrophages and microglial cells [70]. The interaction between cells expressing CD4+ and HIV co-receptors (CXCR4 and CCR5) and infected cells expressing viral

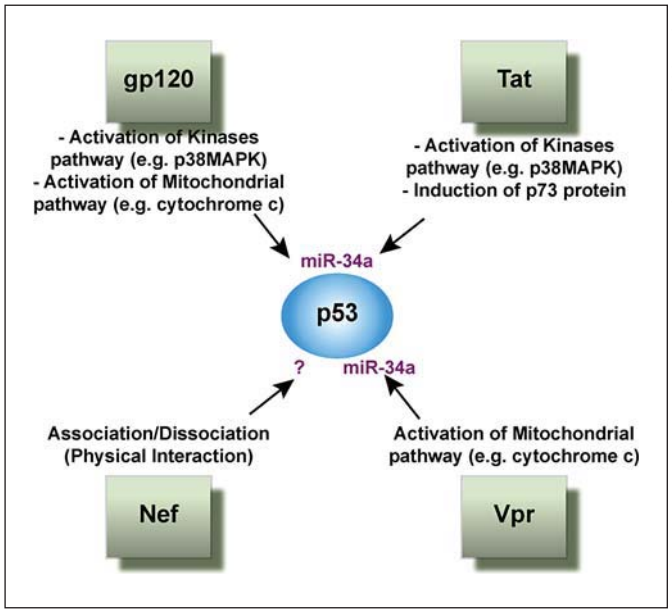

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Fig. 2. p53 activation pathways. Schematic representation of the pathways activated by HIV-1 viral proteins to induce p53 levels. Small non-coding RNAs such as miR-34a are also involved in these pathways in neuronal cells. It is unclear whether Nef protein is also using miRNAs to regulate p53 levels.

envelope glycoprotein at their surface, result in cell fusion and syncytia formation [89]. The formation of syncytia leads to cytopathic effects, including apoptotic pathway activation. It has been shown that an in vitro model regarding the regulation of the mitochondrial pathway of apoptosis in syncytia by p53 is supported by in vivo evidence of the implication of phosphorylated p53, and its target genes Bax and Puma, in the induction of apoptosis in syncytial cells [90]. Therefore, p53 is a likely mediator in the syncytial cell death pathway in the CNS. In an in vitro model of HAND, the addition of soluble gp120 (at 200 pM concentration) to a mixed cerebrocortical culture containing mice neurons, astrocytes and microglia led to a strong activation of p53 [89]. In mixed cerebrocortical cultures from p53-deficient mice exposed to gp120, neurons were resistant to gp120-induced apoptosis [52], suggesting that the p53 pathway is activated in neuronal injury inflicted by gp120.

The analysis of brain tissue of HIV-infected patients with severe dementia shows that p53 is activated in both neuronal and non-neuronal cells [52] and gp120 treatment causes the activation of p53-mediated apoptotic pathway and caspase-3 upregulation in both neurons and microglia [94]. These observations suggest that gp120 neurotoxicity could be mediated via direct interaction with neurons and indirectly via stimulation of microglia to release neurotoxic factors [95]. Additionally, neuronal p53 expression due to neurotoxic factors (viral and host factors released by infected cells) is required for neuronal injury. It has been reported that in a murine neuron/microglia co-culture, the addition of gp120 caused apoptosis when both cells were derived from mice expressing p53. p53–/– cells were resistant to apoptosis regardless of microglial phenotype, and p53-expressing neurons required p53+/+ microglia to undergo gp120-induced apoptosis [52]. These results show that in addition to its role in intrinsic apoptotic pathway, p53 may participate in the proapoptotic tuning of cellular networks in the CNS.

Other evidence supporting the involvement of p53 in the development of HAND came from studies on murine models of HAND and the examination of viral proteins' role in the activation of p53. Notably, it has been shown that in transgenic mice expressing HIV-1 gp120 protein, the neurotoxicity, dendritic damage, and apoptosis are mediated by caspase activation, suggesting that p53 is involved in caspase activity [94]. Another study showed that in severe combined immunodeficient mice grafted with HIV-1_{ADA}-infected monocyte-derived human macrophages, there is an upregulation of glucose synthase kinase 3-β (GSK 3-β), a kinase activating and phosphorylating p53 [96, 97].

Additionally, evidence from in vitro studies suggests that HIV-1 protein Tat also participates in p53-mediated neuronal injury [88]. Activation of p53 was detected in neuronal culture treated with supernatants from HIV-1 Tat-transfected monocytoid cells (Tat supernatant); p53 overexpression can be prevented by prior treatment with growth hormones [98]. Other studies have shown that in astrocytes and neuronal cell lines, the intracellular expression of Tat causes cell cycle arrest via the interaction of Tat with several cell cycle regulators, including p53 and p63 [46]. Although it appears neurons and astrocytes do not harbor HIV-1 infection, it has been reported that Tat can be taken up by neurons and astrocytes [99]. Therefore, it is possible that productively infected cells release Tat, which is then internalized by neurons and astrocytes. Internalized Tat would consequently prevent p53 ubiquitination and subsequent degradation resulting in p53 accumulation and activation [100]. However, it is also possible that p53 activation by Tat is a secondary affect that arises from Tat's neurotoxicity.

In addition to the viral infection of the CNS, indirect consequences of the infection also contribute to the neu-

rodegeneration. The immune profiles within the CNS suggest an immune activation involving mediators produced by activated macrophages, microglia, and astrocytes [101]. The increase in the production of neurotoxic substances – including cytokines such as TNF-α, interleukin (IL-1), chemokines (such as MCP-1 and excitatory amino acids in the brain) – are other components of the neurodegeneration in HAND [102–105]. Beside its direct neurotoxic effect, TNF-α promotes the over-simulation of neuronal excitatory amino acids receptors, which in turn results in mitochondrial dysfunction and the accumulation of reactive oxygen species in the cerebrospinal fluid. The elevated level of cytokines, chemokines, excitatory amino acids, and nitric oxide in the brain lead to excitotoxicity and oxidative stress that, in turn, activate the p53-mediated pathway to apoptosis [106–108]. However, AIDS neuropathogenesis is a lengthy process and might involve sub-lethal neuronal injury resulting in synapse retraction and loss, dendritic pruning, and neural dysfunction [106]. Further, neuronal dysfunction can also involve chronic oxidative stress that could cause sub-lethal DNA damage and activate p53, which in turn induces caspases in axons and dendrites under extensive simulation by excitatory neurotransmitters, a phenomenon that could result in synaptic cell death and dendritic thinning [100]. Other byproducts of the HIV-induced immune activation, such as kainic acid and quinolinic acid, are known to inflict morphological damage to neurons and induce p53 expression in neurons [109, 110].

Lastly, we showed that Tat induces neurite retraction that is p53 mediated [88]. Furthermore, Tat-induced neurite retraction also required p73 and suggests that p53, together with p73, may play a role in maintaining neuronal plasticity. The notion that HIV-1 viral proteins affect neuronal plasticity was demonstrated by other groups. Kitayama et al. [22] showed that Vpr inhibits axonal outgrowth by causing mitochondrial dysfunction in the absence of noticeable apoptosis. Singh et al. [111] also showed that while the neurotoxic affect of Tat is independent of p38MAPK, gp120 induces neurite degeneration through p38MAPK activation. Also, Chauhan et al. [17, 112] reported that Tat inhibits axonal transport. Interestingly, they also showed that the amount of Tat required to inhibit neuronal function was remarkably less than the concentration required to induce LTR transactivation [112]. Considering that p53 also has a role in affecting mitochondrial function [113], as well as interacting with p38MAPK [114], it would be interesting to see if p53 also plays a role in Vpr- and gp120-mediated neurodegeneration.

Finally, p53 is also implicated in other aspects of HIV-1 pathogenesis. For instance, development of non-Hodgkin's lymphoma in AIDS is associated with the suppression of p53 [115]. When present, only mutant forms of p53 were found associated with the lymphoma [116]. Likewise, AIDS-associated development of Kaposi's sarcoma is linked to the suppression of p53 transcriptional activity by LANA (latency-associated nuclear antigen), a viral protein that is highly expressed during latency [117]. Considering that LANA has high immunoreactivity, the development of Kaposi's sarcoma probably occurs when the host immune functions are sufficiently deficient to clear LANA-expressing cells. In such a scenario, cells latently infected with KSHV will suppress p53 activity and promote cell survival and oncogenesis. In agreement with p53 suppression being required for KSHV-associated lymphomas in HIV-1 positive patients, Sarek et al. [118] demonstrated that p53 reactivation induced by disrupting the p53-MDM2-LANA interaction leads to apoptosis.

Involvement of p53 in AD

AD is accompanied by neurodegeneration and neuronal loss in the frontal cortex, leading to cognitive impairment and dementia [89]. Several factors are thought to trigger neurodegeneration in AD, including cytoplasmic accumulation of β-amyloid proteins [119, 120] that may be responsible for inducing endoplasmic reticulum stress and cytoplasmic accumulation of phosphorylated Tau proteins that oligomerize to disrupt the cytoskeletal network [121, 122]. Further, the vast majority of familiar AD cases consist of mutated presenilin-1 and/or presenilin-2 [123].

Regardless of how neuronal injury is triggered, p53 is highly elevated in AD [124, 125]. The elevation and activation of p53 correlates well with the extent of mitochondrial and other dysfunctions. Namely, a decrease in Bcl-2 with increased Bax expression was noted in human neurons treated with β-amyloid peptides [126] and Alzheimer's brains [127, 128]. In the case of Bcl-2, p53-associated miR-34a [91, 129] targets Bcl-2 transcripts for degradation [130]. This observation corroborates our results obtained with HIV-1-Vpr-treated neurons. We were able to reverse this phenomenon by using anti-miR-34a, where we observed the translocation of Bax protein back to the cytoplasm (data not shown).

Furthermore, p53 directly interacts with proapoptotic factors such as Bax and Bak (Bcl-2-antagonist/killer 1) to

permeabilize mitochondrial membranes [131–134] and, together with Drp1 (dynamin-related protein 1), mitochondrial fragmentation [135–137]. Interestingly, Sheridan et al. [138] reported that mitochondrial fragmentation can be induced by Bax/Bak without causing cytochrome c release; thus, it may be possible to sustain mitochondrial dysfunction without triggering apoptosis. Regardless, mitochondrial fragmentation is associated with decreased oxidative metabolic capacity (as measured by succinid dehydrogenase activity) at the synapse [139, 140]. Therefore, it appears that p53 induces/exacerbates mitochondrial dysfunction by upregulating Bax in AD.

Neuronal dysfunctions reported in AD are also attributable to mitochondrial dysfunction. These include synaptic aberrations [141–143], decreased glucose metabolism [144], and defective axonal transport [145, 146], and particularly mitochondrial mislocalization [147]. Interestingly, few of the above neuronal dysfunctions also involve p53. For example, Di Giovanni et al. [40, 148] demonstrated the need for p53 in neurite outgrowth and axonal regeneration [36] that is dependent on CBP/p300 acetylation of Lys 320. p53 is also required for suppressing tumor development through the inhibition of glycolysis [149–152].

Lastly, p53 appears to mediate apoptosis in primary human neurons expressing Aβ1–42 [153]. Microglial apoptosis is also mediated by p53 in AD [154]. Interestingly, a conformational isoform of p53 has been identified to be associated with AD [155], suggesting that p53 is either mutated or misfolded in AD.

Involvement of p53 in PD

In PD, pathology involves neurodegeneration and loss of dopaminergic neurons in the substantia nigra (fig. 1). It initially starts as a movement disorder that progresses into cognitive and language impairment and eventually dementia. As with HAND and AD, elevation of p53 is also seen in PD [31, 156]. p53-mediated neuronal death is observed in both cellular [157] and animal [158] models of PD.

Several genes play a role in suppressing p53 expression and/or transcriptional activity. Surprisingly, three of these genes are associated with autosomal recessive juvenile PD. Namely, loss of parkin function leads to an increase in p53 mRNA levels and transcriptional activity while overexpression of parkin inhibits 6-hydroxydopamine mediated neurotoxicity [159]. Further, Ring1 domain of parkin binds p53 promoter and suppresses its transcriptional activity [159]. Similarly, mutations in DJ-1 are also associated with early-onset juvenile PD [160], while wild-type DJ-1 is also capable of inhibiting p53 transcriptional activity [161] and suppressing Bax expression.

Pink1 (PTEN-induced putative kinase 1) mutation also causes early-onset PD [162]. Functionally, Pink1, together with parkin, induces damaged mitochondria to undergo autophagy or mitophagy [163, 164]. p53-induced genes, Puma and Bax, also mediate mitophagy [165], likely by directly disrupting mitochondrial membrane potential. Therefore, it may be possible that, upon p53 activation, increased Puma/Bax expression damages mitochondria that would signal mitophagy. In the absence of functional Pink1, damaged mitochondria would accumulate, thereby further aggravating the cells towards apoptosis. Considering that the loss of Pink1 function also causes mitophagy while promoting mitochondrial fission [166], it appears that Pink1 may have a role in mitochondrial quality control. Furthermore, these studies illustrate the importance of proper mitochondrial function and turnover in PD and demonstrate how p53 may be a key mediator affecting mitochondrial physiology in neurodegenerative diseases.

Other genes associated with PD also affect p53 function. Namely, Syphilin-1, a binding partner for α-synuclein, inhibits p53 transcriptional activity, particularly caspase-3 expression [167]. It has been suggested that α-synuclein may also have a role in inhibiting p53 activation and transcriptional activity [168]. Considering that the loss of α-synuclein function is associated with PD, and mutant α-synuclein expression serves as a murine model of PD, down-modulating neuronal p53 activity may be therapeutic in PD.

Involvement of p53 in Huntington's Disease

Huntington's disease is a familiar genetic disorder with mutations in the gene Huntingtin (HTT) [169]. The disease mainly attacks the spiny neurons in the caudate and the putamen [170–175], though the substantia nigra and the cortex, among others, are affected by the insertion of trinucleotide repeats (C-A-G) at the 5′-end of the gene [176, 177]. Wild-type HTT consists of <35 glutamine repeats [178]. With increased numbers of glutamine repeats, the disease severity increases as it pertains to the age of onset and the severity of the symptoms [179]. Due to its localization to vesicles within the dendrites and cell body

of neurons, HTT is thought to play a prominent role in vesicle transport [180] as well as mitochondrial transport as evidenced by mHTT antagonizing mitochondrial movement [181], perhaps by forming aggregates that impede mitochondrial movement along microtubules [182]. Additionally, mHTT appears to inhibit mitochondrial complex II consisting mainly of succinic dehydrogenase, as evidenced by significantly impaired complex II in postmortem Huntington's disease brains [183, 184], while mitochondria from cells expressing mHTT demonstrate dysfunction, including decreased membrane potential [185]. Choo et al. [186] also demonstrated increased susceptibility to calcium-induced membrane permeability and cytochrome c release in mitochondria exposed to mHTT.

Apparently, p53 also plays a role in mediating mHTT-induced mitochondrial pathogenesis in Huntington's disease. First, p53 is elevated in the brains of Huntington's disease patients [187], while susceptibility of spiny neurons to mHTT-mediated injury was directly correlated to p53 elevation and indirectly correlated to the endogenous levels of Bcl-2 [188]. mHTT was also found to interact with p53 in the inclusion body, both biochemically [189] and genetically [190]. In fact, considering the possibility that DNA damage precedes mHTT aggregation [191] and reports showing p53 upregulates HTT expression [192], p53 seems to be intimately partnered with mHTT to insult neurons. The notion that mHTT can lead to increased p53 transcriptional activity further suggest how, in Huntington's disease, neuronal injury and mitochondrial dysfunction are exacerbated by p53.

Conclusion

In this review, we established the relation between p53 protein and neurodegenerative diseases. We also showed that p53 functionally interacts with cellular or viral factors and that this interaction leads to mitochondrial deregulation and activation of the caspase pathway, which could promote cell dysfunction and death. These observations render p53 an ideal target for the development of therapeutic approaches that could prevent the development of neuronal deregulation. In this regard, development/design of small molecules/non-coding RNA (e.g. miRNAs) capable of modulating the role of p53 are now being evaluated in cancer clinical trials and to a certain extent in neurodegenerative diseases (www.clinicaltrials.gov). The development and efficacy of these molecules will help in therapeutic interventions and may improve the life quality of patients with neurocognitive disorders.

Further, regulation of p53 may also depend on the cellular microenvironment, and eventually acts to promote cell death or survival depending on the cell type, gene expression profile, protein activity, and the type of stress stimuli, among other criteria such as aging. In this regard, and according to UNAIDS, over 50% of HIV-1 patients are or expected to be over 50 years old in the coming year or two. Therefore, it is important to design a p53 inhibitor(s) to prevent the complications that could arise from the development of neurocognitive disorders. In addition to neurodegenerative diseases, p53 is also implicated in other apoptosis-related diseases, such as cancer, atherosclerosis, and ischemia, which are increasingly recognized to be correlated with aging [193]. Therefore, a therapeutic intervention to inhibit p53 intervention in the development of neurocognitive disorders is highly and urgently recommended.

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