Role of p38 MAPK Signaling in Neurodegenerative Diseases: A Mechanistic Perspective

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Abstract

Neurodegenerative diseases are conditions that result in progressive degeneration and eventually the death of nerve cells. Common neurodegenerative diseases include Alzheimer’s disease (AD), Parkinson’s disease (PD) and amyotrophic lateral sclerosis (ALS) disease. Neurons are lost in specific regions of the brain; in AD, neurodegeneration affects neurons of the cerebral cortex and hippocampus, in PD, it affects neurons of the substantia nigra in the midbrain and in ALS, it affects motor neurons of the motor cortex. Neuronal death is caused by hyper-phosphorylation of various neuronal proteins which is mediated by the activation of the members of the family of mitogen-activated protein kinases (MAPKs) one of which is p38 MAPK. MAPK (p38) signaling pathway is activated by varied stimuli and numerous cellular stressors as it controls a variety of cellular activities such as differentiation, survival, apoptosis, and so on. Deviation from the strict control of MAPK signaling pathway has been implicated in the development of neurodegenerative diseases. Persistent activation of this signaling pathway has been proposed to mediate hyper-phosphorylation in AD, PD, and ALS which then leads to the process of neurodegeneration.

ABBREVIATIONS

AD: Alzheimer’s Disease; PD: Parkinson’s Disease; ALS: Amyotrophic lateral sclerosis

INTRODUCTION

The human body is made up of various systems one of which is the nervous system. This consists of nerve cells (also called neurons). Neurons have organelles and are basic but differ from normal cells in that when they die or are damaged, they can neither be replaced nor repaired. Due to enhanced medical technologies, the average life expectancy has increased which in turn has led to a rapid increase in the elderly population. This increase has led to the ‘aging era’, which is accompanied by social issues such as neurodegeneration [1]. Neurodegeneration has to do with diseases which affect the central nervous system causing progressive nervous system dysfunction. Examples of neurodegenerative diseases include Alzheimer’s disease, Parkinson’s disease [2] and Amyotrophic lateral sclerosis disease [1]. An important aspect of neurodegenerative diseases involves dementias associated with aging [3] also known as senile dementia. Senile dementia is the mental deterioration (loss of intellectual ability) that is associated with old age [4].

A set of networking enzymes and related proteins functions together so that old proteins can be degraded as newly synthesized ones form new structures and connections so that the proper complement of building materials is available [5]. Improper clearance of old proteins is believed to be a contributing factor in neurodegenerative diseases, which are often characterized by the aggregation of misfolded proteins [5] and are therefore classified as proteopathies [6]. Examples of these misfolded proteins include α-synuclein, which can aggregate to form insoluble fibrils in pathological conditions characterized by Lewy bodies in Parkinson’s disease, hyperphosphorylated tau protein which is the main component of neurofibrillary tangles and β-amyloid, the major component of senile plaques which are found in Alzheimer’s disease [6].

Reactive oxygen species (ROS) are normal by-products of mitochondrial respiratory chain activity and can react with membrane lipids, nucleic acids and other macromolecules to cause damage [7]; damaged membranes can induce membrane curvature and extensive tabulation [8]. Over production of these ROS (which is known as oxidative stress) is therefore a central feature of all neurodegenerative disorders as it leads to the damage of neurons. In addition to the generation of ROS, mitochondrial dysfunction plays a role in the pathogenesis of neurodegenerative diseases [9]. Mitochondria are involved with life-sustaining functions including calcium homeostasis, mitochondrial fission and fusion, lipid concentration of the mitochondrial membranes, and the mitochondrial...
permeability transition therefore mitochondrial disease leads to neurodegeneration which involves reduced activity of all these functions [7].

Other known contributing factors to neurodegenerative diseases are axonal swelling and programmed cell death. Axonal swelling has been observed in different neurodegenerative diseases thereby suggesting that defective axons are not only present in diseased neurons, but also that they may cause certain pathological insult due to accumulation of organelles. Axonal transport can be disrupted by a variety of mechanisms including damage to kinesin and cytoplasmic dynein, microtubules and cargoes [10].

Programmed cell death (PCD) which is the death of a cell in any form, mediated by an intracellular program [11] can be activated in neurodegenerative diseases. The form of programmed cell death in multicellular organisms which involves a series of biochemical events leading to characteristic neuronal death is known as neuronal apoptosis. Neuronal apoptotic pathway may occur when factors outside the cell (extrinsic) activate cell surface death receptors (such as Fas) that result in the activation of caspases-8 or -10 or 11 or when there is a mitochondrial release of cytochrome C (intrinsic) or malfunction of endoplasmic reticulum, each leading to the activation of caspase-9 [12].

NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are diseases in which the structure and functions of neurons are progressively lost which eventually leads to the death of neurons from which there is no recovery [1]. These diseases are characterized by loss of neuronal cell function and are often associated with atrophy of the affected nervous system structures (that is neurons) [3]. Neurons are selectively lost in certain regions of the brain that is in cerebral cortex and hippocampus in Alzheimer’s disease, in substantia nigra of the midbrain in Parkinson’s disease, and in motor cortex in amyotrophic lateral sclerosis disease [1].

ALZHEIMER’S DISEASE (AD)

Alzheimer’s disease is the most common form of dementia [5] (it is the cause of 60% to 70% of cases of dementia) [13] and the most common neurodegenerative disorder [5] that usually starts slowly and gets worse over time [13]. The disease was named after a doctor called Alo is Alzheimer who noticed changes in the brain tissue of a woman who had died of strange mental illness in 1906. After she died, he examined her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary, or tau, tangles) which are the main features of AD presently known. About 10% of people over 65 years old and half of those over 85 suffer from AD. Prevalence of this progressive disorder increases with ageing, affecting 3% of people between 60-69-year-olds, 5% of those between 70-79 and 30-50% of those between 80-89 [1].

Alzheimer’s disease begins in the cerebral cortex and hippocampus. The cerebral cortex is involved with thinking, planning and behavior whereas the hippocampus is involved in the formation of new memories. The earliest symptom of AD is a progressive decline in memory [5] followed by problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self-care, and behavioral issues. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life expectancy following diagnosis is 3-9 years [14,15].

Histologically, AD involves loss of synaptic connections resulting in progressive atrophy of the temporal, frontal and parietal lobes of the cerebral cortex. It is characterized by intracellular neurofibrillary tangles (NFTs) and extracellular plaques mainly consisting of hyper-phosphorylated tau protein and beta amyloid (Aβ) respectively [16-18]. In normal adult brain, tau, which is a microtubule-associated protein, plays an important role in the development of neuronal polarity and neuronal processes [19] and binds to microtubules, promoting microtubule assembly and facilitating axonal dynamics in a neuron [20]. When pathologically hyper-phosphorylated, tau molecules are dissociated from microtubules and become insoluble fibrous tangles [1]. NFTs are accumulated in neuronal axons and dendrites thereby leading to degeneration of already-tangled neurons [21].

Aβ is produced through abnormal sequential cleavage of amyloid precursor protein (APP) by the enzymes β- and γ-secretases. Aβ is rarely produced in normal human brain [22], however, when generated, it misfolds into β-sheet conformation in the brain and induces neurodegeneration [23].

PARKINSON’S DISEASE (PD)

Parkinson’s disease is the second most common neurodegenerative disease and the most common neurodegenerative movement disorder [5]. The disease is named after the English doctor James Parkinson, who published the first detailed description of the disease in An Essay on the Shaking Palsy, in 1817. Parkinson’s disease typically occurs in 1% of people over the age of 60, 3.4% of those over 70, and 4% of those over 80 [1]. The symptoms generally come on slowly over time. Early in the disease, the most obvious are shaking, rigidity, slowness of movement, and difficulty with walking. Other symptoms include sensory, sleep and emotional problems, thinking and behavioral problems, abnormal gait and posture, as well as difficulty initiating and completing voluntary and involuntary movements. The average life expectancy following diagnosis is between 7 and 14 years [5].

PD is characterized by intracellular aggregates called Lewy bodies comprising primarily of alpha-synuclein [5]. It involves the loss of dopaminergic neurons of mostly the substantia nigra (a region of the midbrain) accompanied by astrocytosis and increased numbers of microglia. Dopamine is a neurotransmitter vital for normal movements because it allows messages to be transmitted from the substantia nigra to the striatum, which then initiates and controls the ease of movement and balance. Therefore, loss of dopamine causes the neurons in the basal ganglia to fire randomly accounting for involuntary movement and other problems with movement.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic Lateral Sclerosis (ALS) disease is the most fatal neurodegenerative disease that attacks neurons responsible for controlling voluntary muscles [5]. It is a disease in which motor
neurons are selectively targeted for degeneration. The loss of motor neurons in the brain and spinal cord of ALS patients typically results in progressive paralysis and death within a few years of onset [5].

Motor neurons are nerve cells located in the brain, brain stem, and spinal cord that serve as controlling units and vital communication links between the nervous system and the voluntary muscles of the body. Messages from motor neurons in the brain (called upper motor neurons) are transmitted to motor neurons in the spinal cord (called lower motor neurons) and from them to particular muscles. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, and stop sending messages to muscles. Unable to function, the muscles gradually weaken and have very fine twitches. Eventually, the ability of the brain to start and control voluntary movement is lost. The symptoms include fasciculation, cramps, tight and stiff muscles (spasticity), muscle weakness affecting an arm or a leg, slurred and nasal speech, or difficulty chewing or swallowing. These general complaints then develop into more obvious weakness or atrophy.

Histopathologically, ALS is characterized by mutations in the gene encoding Superoxide Dismutase 1 (SOD1) as well as those encoding Transactivation Response DNA-binding protein 43 (TDP-43) [5].

**MITOGEN-ASSOCIATED PROTEIN KINASE (MAPK)**

Mitogen-activated protein kinases (MAPKs) are serine-threonine kinases that mediate intracellular signaling [24]. The mammalian family of mitogen-activated protein kinases (MAPKs) includes extracellular signal-regulated kinase (ERK), p38, and c-Jun NH₂-terminal kinase (JNK). Each of these enzymes exists in several isoforms: ERK1 to ERK8; p38α, -β, -γ, and -δ; and JNK1 to JNK3 [25]. The MAPK signaling pathway consists of at least three components, a MAPK kinase (MAP3K), a MAPK kinase (MAP2K), and a MAPK MAP3Ks phosphorylate and activate MAP2Ks, which in turn phosphorylate and activate MAPKs. The MAPK pathways are activated by diverse extracellular and intracellular stimuli including peptide growth factors, cytokines, hormones, and various cellular stressors such as oxidative stress and endoplasmic reticulum stress (Figure 1) [26]. These signaling pathways regulate a variety of cellular activities including proliferation, differentiation, survival, and death (Figure 1). Deviation from the strict control of MAPK signaling pathways has been implicated in the development of many human diseases including neurodegenerative diseases and various types of cancers. Persistent activation of p38 signaling pathways has been suggested to mediate neuronal apoptosis in AD, PD, HD and ALS, whereas the ERK signaling pathway plays a key role in several steps of tumorigenesis including cancer cell proliferation, migration, and invasion. In this review, recent findings on the roles of MAPK signaling pathways in human disorders are discussed, focusing on neurodegenerative diseases [27].

The cascade of events leading to p38 MAPK activation is extremely conserved all through mammalian tissues including neuronal cells (Figures 1a and 1b). Similar to other MAPKs, the p38 MAPK enzyme is activated by dual phosphorylation of the threonine (Thr) and tyrosine (Tyr) residues in the Thr-Gly-Tyr (TGY) motif situated within the kinase activation loop. Dual phosphorylation at Thr-180 and Tyr-182 residues, by either MAP kinase kinase 3 (MKK3) or MAP kinase kinase 6 (MKK6), induces

![Figure 1 Mitogen-activated protein kinase (MAPK) signaling pathways [26].](image-url)
global conformational reorganizations that modify the alignment of the C- and N-terminal domains of p38 MAPK, consequently permitting the binding of ATP and the desired substrate [28]. The subcellular localization of the p38 MAPK activators MKK3 and MKK6 has been shown using an antibody against a specific peptide present in either MKK3 or MKK6 in addition to over expression of wild-type MKK3 and MKK6-FLAG-tagged proteins. These in vitro experiments in 293T HEK cells showed a similar distribution profile for both the endogenous and exogenous MKK3 and MKK6 proteins in that they are both nuclear and cytoplasmically localized within the cell [29]. The MAP kinase kinase kinases (MKKKs), which are the upstream activators of the MKKs, have been shown in HeLa cells to be activated and localized at the plasma membrane and in the cytoplasm [30].

ROLE OF P38 MAPK PATHWAYS IN ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is a neurodegenerative disease characterized by cognitive and memory dysfunction that is thought to result from the formation in the brain of both senile plaques containing β-amyloid (Aβ) and neurofibrillary tangles containing the microtubule-associated protein tau [31-33]. Tau is present in a hyper-phosphorylated form in neurofibrillary tangles, with its phosphorylation having been shown to be mediated by several kinases including JNK, p38, and ERK [28,34]. Approximately 5% of patients with the familial form of AD harbor mutations in one of the three genes encoding amyloid precursor protein (APP) [35], presenilin-1 [36], or presenilin-2 [37], whereas most cases of sporadic AD are thought to result from multiple gene defects [38]. APP is an integral membrane protein that is cleaved sequentially by α-, β- (also termed BACE1), and γ-secretases to produce non-amyloidogenic or amyloidogenic Aβ proteins [39-41]. Amyloidogenic Aβ is produced by β-secretase-mediated cleavage of APP at amino acid 83, whereas non-amyloidogenic Aβ, which is not toxic to neurons, is generated by γ-secretase-mediated APP cleavage at amino acid 99 [42,43]. Aβ42, a major component of amyloid plaques in the AD brain, is an Aβ peptide with 42 amino acids that is produced by the amyloidogenic pathway. Although most Aβ proteins including Aβ42 and Aβ40 are secreted extracellularly, intracellular Aβ42 has been shown to initiate mitochondrial oxidative stress and has been implicated in the pathogenesis of AD [44,45].

Oxidative stress is thought to be a key risk factor in the development of AD. Such stress is often triggered by Reactive Oxygen Species (ROS) such as the hydroxyl radical, superoxide anion, and hydrogen peroxide and is a typical activator of the p38 MAPK signaling pathway in AD [46,47]. The activated MAPK signaling pathways are thought to contribute to AD pathogenesis through various mechanisms including induction of neuronal apoptosis [48-51] transcriptional and enzymatic activation of β- and γ-secretases, as well as phosphorylation and stabilization of APP, a hallmark of AD [52,53]. ASK1 is a MAPK3 in the p38 MAPK pathway and is activated in response to oxidative stress [54]. Dimerization of APP, which is mediated by the Aβ42 portion of the protein, induces the activation of the ASK1-MKK6-p38 signaling pathway [46,47], resulting in tau phosphorylation. ASK1 also forms a signaling complex with APP, MKK6, JIP1, and JNK1, and it induces either neuronal apoptosis or neurite outgrowth after neural injury [55,56]. Aggregates of Aβ42 induce the activation of microglial macrophages, which then produce ROS and pro-inflammatory cytokines such as TNF-α and IL-1β, all of which stimulate MAPK signaling pathways (Figure 2) [26]. Under conditions of oxidative stress, JNK and p38 are activated and induce the expression of the β-secretase gene, whereas ERK1/2 negatively regulates β-secretase expression (Figure 2) [57]. γ-Secretase is specifically activated by interferon-γ, IL-1β, or TNF-α, and such cytokine-induced γ-secretase activity was found to be blocked by a JNK inhibitor and to be enhanced by the expression of a constitutively active form of MEKK1, implicating the JNK signaling pathway in the regulation of γ-secretase activity [58]. Transforming growth factor-β2 binds to APP, and this binding was shown to initiate APP-dependent apoptosis through the activation of JNK and caspase-3, the extent of cell death induced by mutant APP was markedly greater than that induced by the wild-type protein [59]. Evidence thus suggests that MAPK signaling pathways may contribute to the pathogenesis of AD through the regulation of neuronal apoptosis, β- and γ-secretase activity, and phosphorylation of APP and tau [60]. The physiological role of the p38 MAPK signaling cascade might be involved in the re-organization of the actin cytoskeleton in dendritic spines through different targets. Activity-dependent induction of the p38 MAPK-MK2 axis leading to the phosphorylation of SRF in neurons can potentially trigger the activation of Arc/Arg3.1 transcription (Figure 2a). Given the significance of Arc/Arg3.1 protein in the molecular mechanism underlying synaptic plasticity, in regulating spine morphology and in promoting the stability of the actin network, the knowledge of the precise signaling cascade(s) controlling Arc/Arg3.1 transcription could provide insightful information on the function of this multi talented protein and its function in neurodegenerative disease [61-65]. Activated p38 MAPK-MK2 axis could also potentially regulate Arp2/3 complex via phosphorylation of actin remodeling proteins such as p16-Arc in neurons (Figure 2a), p16-Arc has been shown to interact with and is phosphorylated by MK2 at Ser-77 in vitro [66]. Strong evidence suggests that the Arp2/3 complex is required for changes in dendritic spine morphology as it plays a key role in the formation of branched actin filamentous networks [67-69]. Another potentially important role for p38 MAPK signaling pathway in actin remodeling in neurons is via tau. p38 MAPK-dependent hyper phosphorylation of tau could induce tau mis location from the axon to dendritic spines, where hyperphosphorylated tau is then able to bind to F-actin (Figure 2b) [70]. However further experimental work in neurons is needed not only to validate the p38 MAPK downstream substrates, but also to show their functional importance in remodeling dendritic spines in healthy neurons and in neurodegenerative diseases.

ROLE OF P38 MAPK IN PARKINSON’S DISEASE

Parkinson’s disease (PD) is the second most prevalent neurodegenerative disease after AD. PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra and by the accumulation in the brain of Lewy bodies (LBs), in which specific proteins including modified α-synuclein are deposited. The symptoms of PD include movement disorders such as resting tremors, postural abnormalities, rigidity, and akinesia, all of which develop as a result of the loss of 50 to 70%
Figure 2 Roles of MAPK pathways in Alzheimer’s disease (AD) [26].

Figure 3 p38 MAPK interactions involved in Parkinson’s disease neuropathology and associated neurodegeneration. Neurotoxins viz. rotenone, maneb, paraquat and MPTP evokes numerous detrimental phenotypes in degenerating neurons and p38 MAPK is responsible for microglia activation, induction of oxidative stress, apoptosis, neuroinflammation and neurodegeneration as triggered by these toxins [88].

of dopaminergic neurons [71,72]. To date, mutations in nine genes have been linked to PD. Those in the genes for α-synuclein, ubiquitin carboxyl-terminal hydrolase L1 (UCHL1), leucinerich repeat kinase 2 (LRRK2), GRB10-interacting GYF protein 2 (GIGYF2), and HtrA2 (also known as Omi) are inherited in an autosomal dominant manner, whereas those in the genes for parkin, PTEN-induced kinase 1 (PINK1), DJ-1, and ATP13A2 are responsible for autosomal recessive forms of PD [73]. Three synuclein genes, those for α-, β-, and γ-synucleins, have been identified in humans. α-Synuclein is present in LBs in the brain of PD patients and plays a key role in the development of PD. Pathological forms of α-synuclein, including the mutants A30P, E46K, and A53T, as well as the wild-type protein at high levels that result from duplication or triplication of the α-synuclein
gene, are prone to form aggregates that trigger neuronal apoptosis [74,75]. LBs contain α-synuclein that has been modified by phosphorylation, ubiquitination, nitration, or truncation [60]. The high prevalence of such modified forms of α-synuclein in the brain of PD patients suggests that they might contribute to neuronal toxicity [76]. Increased levels of α-synuclein are thought to be associated with neuronal apoptosis induced by oxidative stress, neuro-inflammation, or dysfunction of MAPK signaling pathway [60].

Oxidative stress is a major cause of neuronal death in PD. Studies have shown that ROS production induced by the toxins results in the activation of microglial cells, which subsequently attack neighboring dopaminergic neurons [77-79]. α-Synuclein activates p38 pathway in human microglial cells, resulting in the production of IL-1β and TNF-α and consequent promotion of inflammation [80]. α-Synuclein also induces the expression of IL-6 and intercellular adhesion molecule-1 (ICAM-1) in human astrocytes and thereby promotes chronic inflammation. The up-regulation of these latter two proteins is also associated with the activation of MAPK signaling pathway [80]. Moreover, induction of both the release of cytokine c from mitochondria and mitochondrial oxidative stress appears to contribute to the regulation of neuronal apoptosis by α-synuclein [81,82]. Human LRRK2 is a 280-kDa protein that contains several functional domains including leucine-rich repeats, a Ras-related GTPase domain, a MAP3K domain, and WD-40 repeats [83]. Even though several mutations in the Ras-related GTPase and MAP3K domains of LRRK2 have been associated with familial or sporadic PD [84]. LRRK2 was recently found to possess MAP3K activity for MAP2Ks. Parkin is a multi domain E3 ubiquitin ligase that mediates the ubiquitination of several substrates including cyclin E, synphilin, and LIM kinase 1. It also protects dopaminergic neurons from several neurotoxins and oxidative stress [85,86].

Together, these various observations suggest that MAPK signaling pathway contribute to neuro-inflammatory responses and neuronal death triggered by α-synuclein aggregates or functional deficiencies in parkin in the pathogenesis of PD [60]. Additionally, it has been observed that amplified α-synuclein levels are linked to an increase in neuro-inflammation as it has been shown that α-synuclein activates p38 MAPK and other MAPKs in glial cells, a finding that is supported by the fact that extracellular α-synuclein released from damaged neurons interacts with microglia [87]. As described above, the activation of glial cells through the p38 MAPK-MK2 cascade consequently results in the production of inflammatory cytokines and TNF-α, which can induce and promote neuro-inflammation as a physiological neuroprotective mechanism. If the glial cells become over activated, however, as may occur through elevated levels of extracellular α-synuclein released from damaged Lewy body containing neurons, then chronic inflammation could be established and lead to neuronal cell death. Neuro-inflammation in PD is a chronic mechanism that could be linked with the modification of glial cells, comprising astrocytes and microglia. Microglia activation in PD brains acutely contains a panel of microgial-derived neurotoxic factors such as reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), elevated pro-inflammatory cytokine levels, and upregulated inflammatory-associated factors such as cyclooxygenase-2, which altogether cooperate to stabilize microglial response in PD brains (Figure 3) [88]. Hence, the continued use of anti-inflammatory drugs can indeed reduce the risk for the disease. The neuronal response to microglia activation triggers unwanted trauma viz. oxidative stress (OS), neuro-inflammation, cytokine-receptor-mediated apoptosis, which eventually contribute to DA neuronal mortality and subsequent disease progression. Remarkably, recent reports on transgenic mice related model mice were supportive of the idea that neuro-inflammation in PD can be ambiguous, that is protective in the initial stages of degeneration but becomes severely damaging as the disease progresses [89-91].

ROLE OF P38 MAPK IN AMYOTROPHIC LATERAL SCLEROSIS DISEASE

Amyotrophic lateral sclerosis (ALS, also called Lou Gehrig’s disease) is a progressive degenerative disease characterized by a selective loss of motor neurons that results in muscle atrophy, paralysis, and, eventually, death [92,93]. Most cases of ALS are sporadic, with ~10% of cases being inherited in a dominant manner as a result of a familial mutation in the gene for Cu/Zn superoxide dismutase (also known as superoxide dismutase 1, or SOD1). Recent studies have also implicated the nuclear acid-binding proteins TDP-43 (TAR DNA-binding protein-43) [94] and FUS (fused in sarcoma; also known as TLS, for translated in liposarcoma) in the pathogenesis of ALS, suggesting that a defect in RNA metabolism may be a contributing factor [95]. SOD1 is a metalloenzyme that catalyzes conversion of the superoxide anion to hydrogen peroxide [96]. It is thought that ALS-associated mutations result in a neurotoxic gain-of-function of SOD1 [97]. Aberrant expression and activation of p38 MAPK in motor neurons and microglia are thought to be important for ALS progression [98]. Moreover, a p38 MAPK inhibitor, SB203580, prevents the apoptosis of motor neurons induced by mutant SOD1 [99]. Both p38 and JNK1 are also implicated in cytoskeletal abnormalities of spinal motor neurons, a feature of familial and sporadic ALS, through aberrant phosphorylation and consequent aggregation of neurofilaments [100-102]. Exogenous NO also induces expression of Fas ligand (FasL) and thereby stimulates Fas signaling, which triggers activation of the p38 pathway and NO synthesis [60]. SOD1 mutants including A4V, G85R, and G93A interact with Derlin-1, a component of the ER-associated degradation machinery [103], resulting in the activation of the ASK1-mediated cell death pathway in motor neurons [104]. ASK1 is associated with the mechanism of ER stress-induced neuronal cell death [105,106] (Figure 4).

CONCLUSION

Considerable progress has been made in the understanding of the functional role of the p38 MAPK signaling cascade in synaptic plasticity in the hippocampus and its potential role in neurodegenerative diseases such as AD, PD and ALS. The p38 MAPK signaling pathway has been implicated in the pathogenesis of neurodegenerative diseases. In AD, it causes the phosphorylation of APP and hyper-phosphorylation of tau protein. In PD, it causes neuronal death triggered by α-synuclein aggregates. In ALS, it is causes aberrant phosphorylation of neurofilaments in motor neurons and microglia which results in neuronal death. Therefore, persistent activation of the p38
signaling pathways has been seen to mediate neuronal apoptosis thereby leading to neurodegeneration in AD, PD and ALS disease.

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