Biochimica et Biophysica Acta 1802 (2010) 396–405

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Pathological roles of MAPK signaling pathways in human diseases

Eun Kyung Kim, Eui-Ju Choi *

School of Life Sciences and Biotechnology, Korea University, Seoul 136-701, South Korea

ARTICLE INFO

Article history:
Received 10 September 2009
Received in revised form 26 November 2009
Accepted 1 December 2009
Available online 14 January 2010

Keywords:
MAPK
JNK
p38
Neurodegenerative disease
Cancer

ABSTRACT

The mammalian family of mitogen-activated protein kinases (MAPKs) includes extracellular signal-regulated kinase (ERK), p38, and c-Jun NH_2-terminal kinase (JNK), with each MAPK signaling pathway consisting of at least three components, a MAPK kinase kinase (MAP3K), a MAPK kinase (MAP2K), and a MAPK. 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. These signaling pathways regulate a variety of cellular activities including proliferation, differentiation, survival, and death. Deviation from the strict control of MAPK signaling pathways has been implicated in the development of many human diseases including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and various types of cancers. Persistent activation of the JNK or p38 signaling pathways has been suggested to mediate neuronal apoptosis in AD, PD, 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, we summarize recent findings on the roles of MAPK signaling pathways in human disorders, focusing on cancer and neurodegenerative diseases including AD, PD, and ALS.

1. Introduction

Mitogen-activated protein kinases (MAPKs) are serine-threonine kinases that mediate intracellular signaling associated with a variety of cellular activities including cell proliferation, differentiation, survival, death, and transformation [1–3]. The mammalian MAPK family consists of extracellular signal-regulated kinase (ERK), p38, and c-Jun NH_2-terminal kinase (JNK; also known as stress-activated protein kinase or SAPK). Each of these enzymes exists in several isoforms: ERK1 to ERK8; p38-α, -β, -γ, and -δ; and JNK1 to JNK3 [3,4]. Each MAPK signaling axis comprises at least three components: a MAPK kinase kinase (MAP3K), a MAPK kinase (MAP2K), and a MAPK. MAP3Ks phosphorylate and activate MAP2Ks, which in turn phosphorylate and activate MAPKs (Fig. 1A). Activated MAPKs phosphorylate various substrate proteins including transcription factors such as Elk-1, c-Jun, ATF2, and p53. MAPK pathways are activated either as a result of a series of binary interactions between the kinase components or through the formation of a signaling complex containing multiple kinases that is guided by a scaffold protein. Such scaffold proteins mediate the activation of MAPK signaling pathways consisting of specific kinase components. Kinase suppressor of Ras-1 (KSR) and MEK partner 1 (MP1) function as scaffold proteins for the ERK signaling pathway, whereas JNK-interacting proteins (JIPs) serve as scaffold proteins for the JNK pathway. β-Arrestin 2 acts as a scaffold protein for both the ERK and JNK signaling pathway [5,6] (Fig. 1B).

The JNK and p38 signaling pathways are activated by pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β or in response to cellular stresses such as genotoxic, osmotic, hypoxic, or oxidative stress (Fig. 1A). The JNK pathway consists of JNK, a MAP2K such as SEK1 (also known as MKK4) or MKK7, and a MAP3K such as ASK1, MEKK1, mixed-lineage kinase (MLK), or transforming growth factor-β-activated kinase 1 (TAK1) [7]. In the p38 signaling pathway, distinct MAP2Ks such as MKK3 and MKK6 activate p38 and are themselves activated by the same MAP3Ks (such as ASK1 and TAK1) that function in the JNK pathway. In the ERK signaling pathway, ERK1 or ERK2 (ERK1/2) is activated by MEK1/2, which in turn is activated by a Raf isoform such as A-Raf, B-Raf, or Raf-1 (also known as C-Raf). The kinase Raf-1 is activated by the small GTPase Ras, whose activation is mediated by the receptor tyrosine kinase (RTK)-Grb2-SOS signaling axis [3]. Members of the Ras family of proteins, including K-Ras, H-Ras, and N-Ras, play a key role in transmission of extracellular signals into cells [8].

Abbreviations: MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH_2-terminal kinase; MAP3K, MAPK kinase kinase; MAP2K, MAPK kinase; KSR, kinase suppressor of Ras-1; MP1, MEK partner 1; JIP, JNK-interacting protein; TNF, tumor necrosis factor; IL, interleukin; MLK, mixed-lineage kinase; RTK, receptor tyrosine kinase; ASK1, apoptosis signal-regulating kinase 1; ROS, reactive oxygen species; LPS, lipopolysaccharide; ER, endoplasmic reticulum; AD, Alzheimer's disease; Aβ, amyloid-β; APP, amyloid precursor protein; PD, Parkinson's disease; LB, Lewy body; LRRK2, leucine-rich repeat kinase 2; PINK1, PTEN-induced kinase 1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; iNOS, inducible NO synthase; TTRAP, TRAF- and TNF receptor-associated protein; ALS, amyotrophic lateral sclerosis; SOD1, superoxide dismutase 1; TDP-43, TAR DNA-binding protein-43; FUS, fused in sarcoma; TLS, translated in liposarcoma; FasL, Fas ligand; EGFR, epidermal growth factor receptor

* Corresponding author. Tel.: +82 2 3290 3446.
E-mail address: ejchoi@korea.ac.kr (E.-J. Choi).

0925-4439/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbadis.2009.12.009

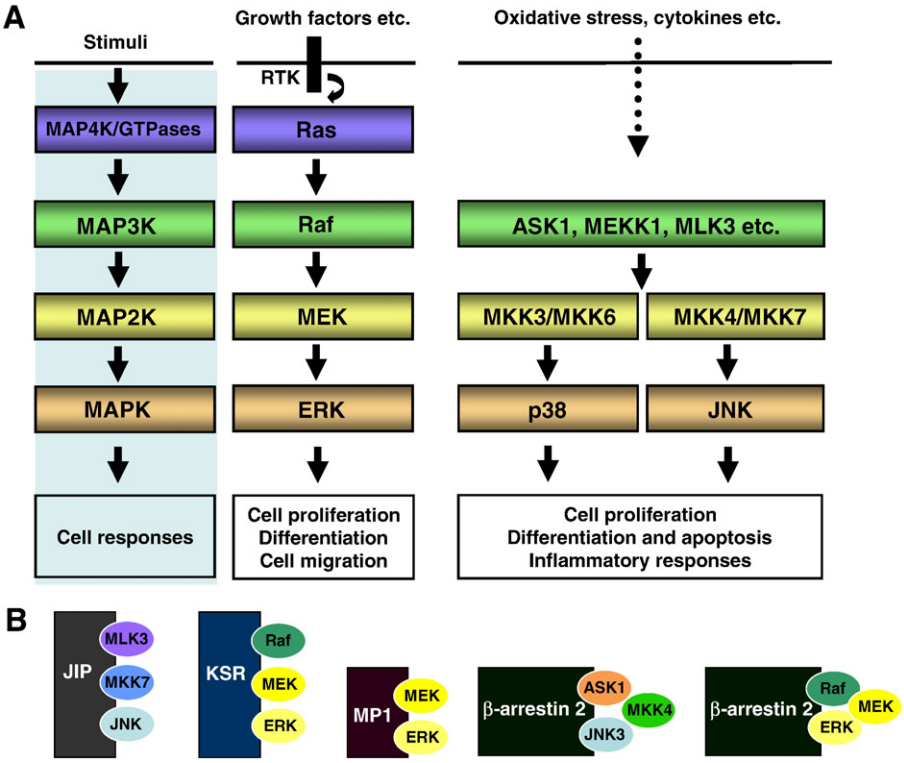


Fig. 1. Mitogen-activated protein kinase (MAPK) signaling pathways. A. MAPK signaling pathways mediate intracellular signaling initiated by extracellular or intracellular stimuli. MAP3Ks, which are activated by MAP4Ks or GTPases, mediate phosphorylation and activation of MAP2Ks, which in turn phosphorylate and activate MAPKs. Activated MAPKs phosphorylate various substrate proteins including transcription factors, resulting in regulation of a variety of cellular activities including cell proliferation, differentiation, migration, inflammatory responses, and death. The mammalian MAPK family includes ERK, p38, and JNK. In the ERK signaling pathway, ERK1/2 is activated by MEK1/2, which is activated by Raf. Raf is activated by the Ras GTPase, whose activation is induced by RTKs such as the epidermal growth factor receptor. The p38 and JNK pathways consist of a MAP3K such as ASK1, MEKK1, or MLK3 as well as a MAP2K such as MKK3 or MKK6 for the p38 pathway or MKK4 or MKK7 for the JNK pathway. Activation by MAPK signaling cascades is achieved either through a series of binary interactions among the kinase components or through formation of a multiple kinase complex mediated by a scaffold protein. B. Scaffold proteins that facilitate activation of MAPK signaling pathways include JIP for the JNK signaling pathway, KSR and MP1 for the ERK signaling pathway, and β-arrestin 2 for the ERK and JNK pathways.

Among the MAP3Ks, MEKK1 possesses not only a kinase activity for phosphorylation of a MAP2K in the JNK or ERK signaling pathways but also an E3 ubiquitin ligase activity that is attributable to its RING domain. MEKK1 regulates cell adhesion and migration through binding to several proteins such as RhoA, Rac, and actin [9]. Tumor cell dissemination and lung metastasis were found to be substantially delayed in MEKK1 knockout mice [10]. Apoptosis signal-regulating kinase 1 (ASK1), a MAP3K in both the JNK and p38 signaling pathways, is activated in response to a variety of stressors including reactive oxygen species (ROS), lipopolysaccharide (LPS), endoplasmic reticulum (ER) stress, and Ca^{2+} influx [11].

Consistent with their critical roles in key cellular activities, including cell proliferation, differentiation, and survival or death, the MAPK signaling pathways have been implicated in the pathogenesis of many human diseases. In this review, we summarize recent findings on the roles of MAPK signaling pathways in human disease, especially cancer and neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

2. MAPK signaling in neurodegenerative diseases

2.1. 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 amyloid-β (Aβ) and neurofibrillary tangles containing the microtubule-associated protein tau [12–14] (Fig. 2A).

Tau is present in a hyperphosphorylated form in neurofibrillary tangles, with its phosphorylation having been shown to be mediated by several kinases including JNK, p38, and ERK [15,16]. Approximately 5% of patients with the familial form of AD harbor mutations in one of the three genes encoding amyloid precursor protein (APP) [17], presenilin-1 [18], or presenilin-2 [19], whereas most cases of sporadic AD are thought to result from multiple gene defects [20]. 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 [21–23] (Fig. 2A). 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 α-secretase-mediated APP cleavage at amino acid 99 [24,25]. $Aβ_{42}$, 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 $Aβ_{42}$ and $Aβ_{40}$ are secreted extracellularly, intracellular $Aβ_{42}$ has been shown to initiate mitochondrial oxidative stress and has been implicated in the pathogenesis of AD [26,27].

Oxidative stress is thought to be a key risk factor in the development of AD [28,29]. Such stress is often triggered by ROS such as the hydroxyl radical, superoxide anion, and hydrogen peroxide and is a typical activator of the JNK and p38 signaling pathways in AD [30,31]. The activated MAPK signaling pathways are thought to contribute to AD pathogenesis through various mechanisms including induction of neuronal apoptosis [32–35],

transcriptional and enzymatic activation of β- and γ-secretases [36,37], as well as phosphorylation and stabilization of APP, a hallmark of AD, by JNK [38,39].

As mentioned above, ASK1 is a MAP3K in the JNK and p38 MAPK pathways and is activated in response to oxidative stress [40]. Dimerization of APP, which is mediated by the $A\beta_{42}$ portion of the protein, induces the activation of the ASK1-MKK6-p38 signaling pathway (Fig. 2B), resulting in tau phosphorylation [41]. ASK1 also forms a signaling complex with APP, MKK6, JIP1, and JNK1 in the brain of APP transgenic mice, and it induces either neuronal apoptosis or neurite outgrowth after neural injury [42,43].

Aggregates of $A\beta_{42}$ 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 (Fig. 2C). 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 [44] (Fig. 2D). 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 [45]. 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 [46].

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.

2.2. 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% of dopaminergic neurons [47,48].

To date, mutations in nine genes have been linked to PD. Those in the genes for α-synuclein, ubiquitin carboxyl-terminal hydrolase L1 (UCHL1), leucine-rich 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 [49].

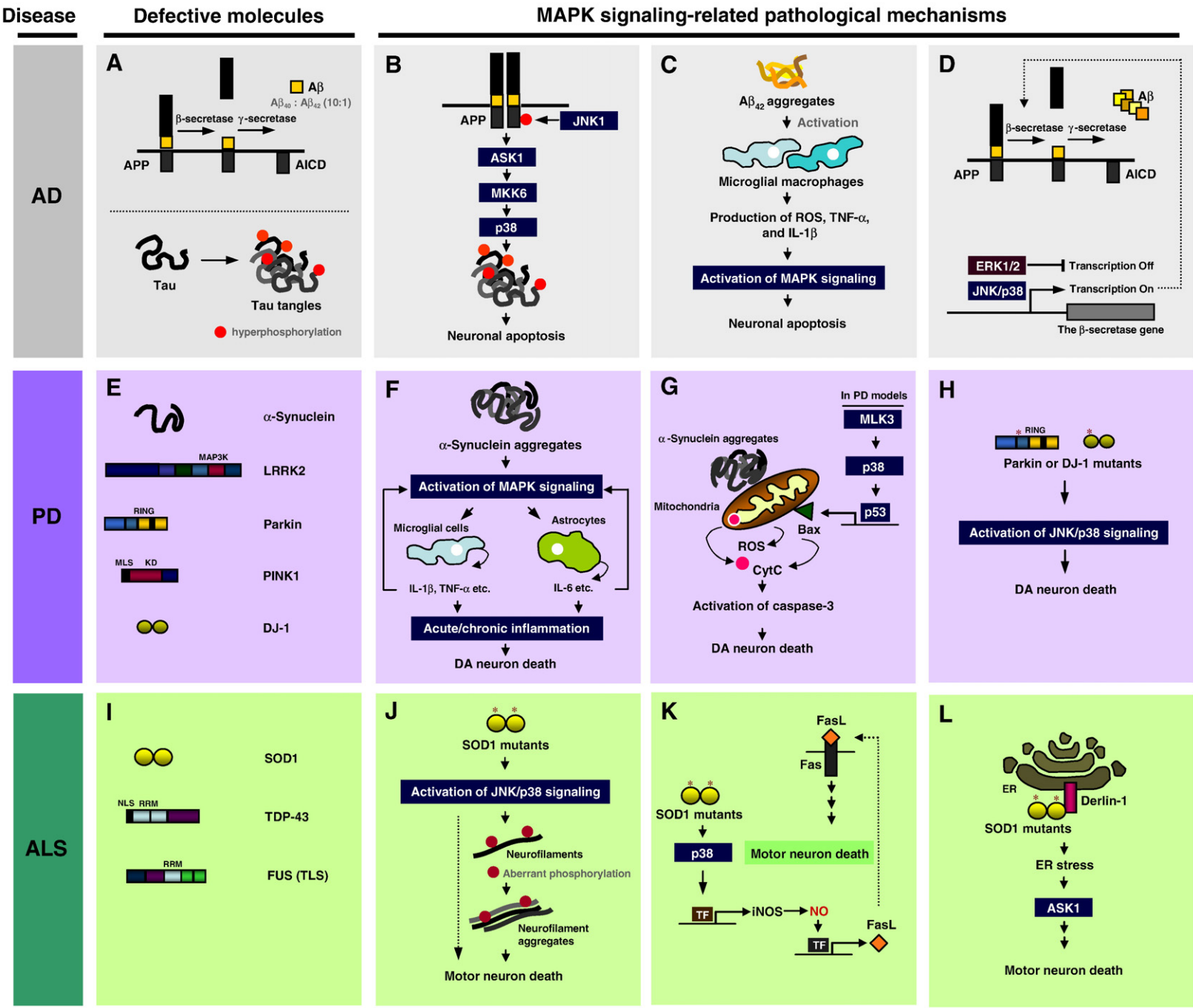
Three synuclein genes, those for α-, β-, and γ-synucleins, have been identified in humans. α-Synuclein is present in LBs in the brain of PD patients and plays a key role in the development of PD [50], although its cellular functions remain unclear. Mice lacking α-synuclein manifest only mild abnormalities in neurotransmission [51]. However, 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 [52–54].

LBs contain α-synuclein that has been modified by phosphorylation [55,56], ubiquitination [57], nitration [58], or truncation [59]. The high prevalence of such modified forms of α-synuclein in the brain of PD patients suggests that they might contribute to neuronal toxicity [60]. Increased levels of α-synuclein are thought to be associated with neuronal apoptosis induced by oxidative stress, neuroinflammation, or dysfunction of MAPK signaling pathways [61–63].

Oxidative stress is a major cause of neuronal death in PD. Studies with animal models of PD based on the neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine, both of which elicit PD-like symptoms, have shown that ROS production induced by the toxins results in the activation of microglial cells, which subsequently attack neighboring dopaminergic neurons [64–66]. α-Synuclein activates p38, ERK, and JNK pathways in human microglial cells, resulting in the production of IL-1β and TNF-α and consequent promotion of inflammation [67]. α-Synuclein also induces the expression of IL-6 and intercellular adhesion molecule-1 (ICAM-1) in human astrocytes and thereby promotes chronic inflammation (Fig. 2F). The up-regulation of these latter two proteins is also associated with the activation of MAPK signaling pathways [68]. Moreover, induction of both the release of cytochrome *c* from mitochondria and mitochondrial oxidative stress appears to contribute to the regulation of neuronal apoptosis by α-synuclein [69,70] (Fig. 2G).

MPTP, a neurotoxin, and pesticides such as rotenone and paraquat have been widely used to elucidate the pathological mechanisms of dopaminergic neuronal death in cellular and animal models of PD [71,72]. Since the genetic relevance of PD occurrence is much lower than its environmental causes at aged population, the exposure of the widely used pesticides such as rotenone and paraquat has been considered as a risk factor for PD [73,74]. Furthermore, Rotenone, but not MPTP, can induce LB-like cytoplasmic inclusions in the substantia nigra neurons [75]. MPTP induces the activation of ASK1 and thereby positively regulates the JNK signaling pathway in dopaminergic neurons [76,77]. 6-Hydroxydopamine, another neurotoxin that elicits the death of dopaminergic neurons in animal models of PD, also induces the activation of ASK1 in dopaminergic cells [78]. The p38 MAPK has also been shown to be activated in PD models and is implicated in the mechanism of neuronal cell death [79,80]. Indeed,

Fig. 2. Roles of MAPK pathways in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). A. APP is sequentially cleaved by β- and γ-secretases to produce the amyloidogenic Aβ proteins $A\beta_{40}$ and $A\beta_{42}$ in the ratio of 10:1. AICD, APP intracellular domain. Neurofibrillary tangles found in the AD brain contain the microtubule-associated protein tau that has been hyperphosphorylated by several kinases including JNK, p38, and ERK. B. APP dimerization, which is mediated by the Aβ portion of the protein, activates the ASK1-MKK6-p38 cascade, which in turn phosphorylates tau, resulting in the formation of neurofibrillary tangles. JNK mediates the phosphorylation of APP, with the stabilization of phosphorylated APP being a hallmark of AD. C. Aggregates of $A\beta_{42}$ activate microglial macrophages, which produce ROS and pro-inflammatory cytokines such as TNF-α and IL-1β, which together trigger activation of the JNK and p38 signaling cascades that may underlie the induction of neuronal death. D. Oxidative stress results in the activation of JNK and p38, which in turn increases transcription of the β-secretase gene. In contrast, ERK1/2 negatively regulates β-secretase expression. β-Secretase activity promotes the production of Aβ. E. PD has been associated with functional defects in several genes. The products of these PD-linked genes include α-synuclein, LRRK2, parkin, PINK1, and DJ-1. RING, a domain with E3 ubiquitin ligase activity; MLS, mitochondrial localization signal; KD, kinase domain. F. α-Synuclein aggregates activate MAPK signaling, which mediates the induction of the pro-inflammatory cytokines IL-1β and TNF-α in microglia. α-Synuclein also induces the expression of IL-6 in astrocytes, resulting in chronic inflammation. These various cytokines may induce the death of neighboring dopaminergic (DA) neurons. G. α-Synuclein aggregates trigger ROS production by mitochondria as well as the release of cytochrome *c* (CytC) from these organelles into the cytosol, resulting in the activation of the caspase cascade and induction of apoptosis, in dopaminergic neurons. The p38 MAPK pathway mediates the activation of p53, which then mediates induction of the pro-apoptotic protein Bax, which in turn promotes permeabilization of the mitochondrial outer membrane. H. Mutants of parkin and DJ-1 activate the JNK or p38 signaling pathways to induce the death of dopaminergic neurons. I. Mutations in the genes for Cu/Zn superoxide dismutase (SOD1), TDP-43, and FUS (TLS) have been associated with ALS. NLS, nuclear localization signal; RRM, RNA recognition motif. J. SOD1 mutants induce the activation of the JNK or p38 signaling pathways, resulting in aberrant phosphorylation and consequent aggregation of neurofilaments, in motor neurons. K. Expression of SOD1 mutants in transgenic mice results in the persistent activation of p38 signaling in motor neurons. Activated p38 induces the expression of iNOS and consequent production of NO, which in turn results in transcriptional activation of the FasL gene, up-regulation of Fas signaling, and cell death. TF, transcription factor. L. SOD1 mutants interact with Derlin-1, a component of the ER-associated degradation machinery, resulting in the activation of the ASK1-mediated cell death pathway in motor neurons.


Disease
Defective molecules
MAPK signaling-related pathological mechanisms
AD
PD
ALS
A
Aβ
Aβ40 : Aβ42 (10:1)
β-secretase γ-secretase
APP
AICD
Tau
Tau tangles
hyperphosphorylation
B
APP
JNK1
ASK1
MKK6
p38
Neuronal apoptosis
C
Aβ42 aggregates
Activation
Microglial macrophages
Production of ROS, TNF-α, and IL-1β
Activation of MAPK signaling
Neuronal apoptosis
D
Aβ
β-secretase γ-secretase
APP
AICD
ERK1/2
Transcription Off
JNK/p38
Transcription On
The β-secretase gene
E
α-Synuclein
MAP3K
LRRK2
RING
Parkin
MLS KD
PINK1
DJ-1
F
α-Synuclein aggregates
Activation of MAPK signaling
Microglial cells
Astrocytes
IL-1β, TNF-α etc.
IL-6 etc.
Acute/chronic inflammation
DA neuron death
G
In PD models
MLK3
p38
p53
α-Synuclein aggregates
Mitochondria
Bax
ROS
CytC
Activation of caspase-3
DA neuron death
H
RING
Parkin or DJ-1 mutants
Activation of JNK/p38 signaling
DA neuron death
I
SOD1
NLS RRM
TDP-43
RRM
FUS (TLS)
J
SOD1 mutants
Activation of JNK/p38 signaling
Neurofilaments
Aberrant phosphorylation
Neurofilament aggregates
Motor neuron death
K
FasL
Fas
SOD1 mutants
p38
Motor neuron death
TF
iNOS
NO
TF
FasL
L
ER
Derlin-1
SOD1 mutants
ER stress
ASK1
Motor neuron death

p38 phosphorylates the tumor suppressor p53, which then induces the expression of the pro-apoptotic protein Bax, which in turn induces the permeabilization of the mitochondrial outer membrane [81], in dopaminergic neurons of the ventral midbrain in mice [82] (Fig. 2G). A role for JNK in neuronal apoptosis has also been widely investigated in both in vitro and in vivo models of PD [83,84]. Rotenone induces apoptosis in dopaminergic SH-SY5Y cells through the activation of JNK and p38 MAPKs [85] and its toxicity is prevented by basic fibroblast growth factor (bFGF), which activates the ERK1/2 and phosphoinositide 3-kinase (PI3K) signaling pathways [86]. Paraquat (1,1′-dimethyl-4,4′-bipyridium), which is chemically similar to MPTP, also triggers dopaminergic cell death through the activation of the JNK pathway [87–89]. Mice deficient in JNK3 are more resistant to MPTP than their wild-type littermates, suggesting that JNK inhibitors might prove effective as therapeutic drugs for PD [90]. The pan-MLK inhibitor CEP-1347 promotes cell survival in several dopaminergic neuronal systems [91]. Although a clinical trial revealed CEP-1347 to be ineffective for the treatment of patients with early PD [92], MLK and JNK inhibitors may still hold promise as drugs to alleviate the symptoms of PD [91,93].

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 [94]. Even though several mutations in the Ras-related GTPase and MAP3K domains of LRRK2 have been associated with familial or sporadic PD [95–97], the contribution of each mutation to the disease process remains unclear. LRRK2 was recently found to possess MAP3K activity for MAP2Ks including MKK3/6 and MKK4/7 in vitro [98]. Further clarification of the biological functions of LRRK2 may provide greater insight into its role in the pathogenesis of PD.

Parkin is a multidomain E3 ubiquitin ligase [99] that mediates the ubiquitination of several substrates including cyclin E [100], synphilin [101], and LIM kinase 1 [102]. It also protects dopaminergic neurons from several neurotoxins and oxidative stress [103,104]. JNK1 is highly activated in dopaminergic neurons expressing loss-of-function mutants of parkin in *Drosophila*, resulting in neuronal death. Indeed, parkin prevents neuronal apoptosis through inhibition of the JNK signaling pathway in a manner dependent on its E3 ligase activity [105]. The neuroprotective function of parkin has also been suggested to result from its selective recruitment to damaged mitochondria, where it promotes the autophagic removal of the ROS-generating organelles [106,107]. Thus, parkin appears to be involved in the regulation of mitochondrial turnover.

Deletion or down-regulation of the expression of the parkin gene has been associated with several human cancers including the breast, ovary, lung, and hepatocellular carcinomas, suggesting that parkin may function as a tumor suppressor [108,109]. In the human brain, parkin forms a complex with PINK1 and DJ-1 that degrades misfolded proteins [110,111]. In addition, parkin compensates for mitochondrial dysfunction associated with PINK mutants in *Drosophila*, suggestive of genetic interaction between PINK1 and parkin [112].

DJ-1 is a neuroprotective protein that has both peroxidase and transcriptional co-activator activities [113,114]. DJ-1 translocates to mitochondria and protects neurons in the cellular response to oxidative stress [115]. It also regulates the aggregation of α-synuclein, with the expression of DJ-1 mutants having been found to promote α-synuclein aggregation and toxicity [116]. In addition, DJ-1 regulates inflammatory responses in astrocytes. DJ-1-deficient astrocytes thus produce 10 times as much nitric oxide (NO) in response to LPS as do wild-type cells. The p38 signaling pathway mediates the up-regulation of inducible NO synthase (iNOS) by LPS [117]. DJ-1 also inhibits the JNK signaling pathway by directly targeting MEKK1 [118]. Furthermore, TRAF- and TNF receptor-associated protein (TTRAP), which protects cells from apoptosis induced by proteasome impairment, has been found to associate with DJ-1. A DJ-1 mutant (M26I/L166P) that binds to TTRAP to a greater extent than does wild-type DJ-1, blocked the protective activity of TTRAP by triggering the activation of JNK1 and p38 in a TTRAP-dependent manner [119].

HtrA2 (or Omi) is a mitochondrial serine protease [120]. Characterization of HtrA2 knockout mice has revealed that this protein has a neuroprotective function [121]. The G399S mutation of HtrA2 results in a decrease in protease activity and has been associated with sporadic PD [122]. The role of HtrA2 in the PINK1-parkin pathway is unclear, however [123]. PINK1 functionally interacts with HtrA2 to protect dopaminergic neurons from apoptosis induced by oxidative stress. HtrA2 is phosphorylated on serine-142 by p38-γ, and the extent of this phosphorylation was found to be reduced in PD patients with the PINK1 mutations C573R and Y431H, suggesting that the PINK1-dependent phosphorylation of HtrA2 might regulate its protease activity [124].

Together, these various observations suggest that MAPK signaling pathways contribute to neuroinflammatory responses and neuronal death triggered by α-synuclein aggregates or functional deficiencies in parkin or DJ-1 in the pathogenesis of PD.

3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's disease) is a progressive neurodegenerative disease characterized by a selective loss of motor neurons that results in muscle atrophy, paralysis, and, eventually, death [125,126]. 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) (Fig. 2I). Recent studies have also implicated the nucleic acid-binding proteins TDP-43 (TAR DNA-binding protein-43) [127] and FUS (fused in sarcoma; also known as TLS, for translated in liposarcoma) [128] in the pathogenesis of ALS, suggesting that a defect in RNA metabolism may be a contributing factor [129]. However, the functions of TDP-43 and FUS in neurons remain unclear.

SOD1 is a metalloenzyme that catalyzes conversion of the superoxide anion to hydrogen peroxide [130]. It is unclear why mutation of the SOD1 gene specifically causes the death of motor neurons, but it is thought that such ALS-associated mutations result in a neurotoxic gain-of-function of SOD1 [131].

Aberrant expression and activation of p38 MAPK in motor neurons and microglia are thought to be important for ALS progression [132]. Persistent activation of p38 correlates with degeneration of motor neurons in transgenic mice expressing the G93A mutant of SOD1 [133,134]. Moreover, a p38 MAPK inhibitor, SB203580, prevents the apoptosis of motor neurons induced by mutant SOD1 [135]. 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 [136–138] (Fig. 2J).

Signaling by p38 MAPK mediates Fas-dependent apoptosis through up-regulation of NO production in motor neurons [139,140]. Exogenous NO also induces expression of Fas ligand (FasL) and thereby stimulates Fas signaling, which triggers activation of the p38 pathway and NO synthesis (Fig. 2K). Motor neurons of transgenic mice expressing mutant SOD1 (G93A or G85R) are more sensitive to NO than are those of control mice.

SOD1 mutants including A4V, G85R, and G93A interact with Derlin-1, a component of the ER-associated degradation machinery [141], resulting in the activation of the ASK1-mediated cell death pathway in motor neurons [142] (Fig. 2L). ASK1 is associated with the mechanism of ER stress-induced neuronal cell death [143]. The pathological mechanisms of MAPK signaling in ALS are summarized in Fig. 2I–L.

4. MAPK signaling in cancer

Many of the cancer-associated mutations of components of MAPK signaling pathways have been found in Ras and B-Raf, both of which participate in the ERK signaling pathway [3,144]. Mutations of K-Ras occur frequently in many human cancers including those of the lung and colon [145]. Indeed, K-Ras mutations have been detected in ~50% of colon cancers, in which mutations of N-Ras are rare [8]. Transgenic mice expressing an activated form (G12D) of K-Ras manifest MEK-dependent hyperproliferation of colonic epithelial cells, whereas expression of the corresponding activated form (G12D) of N-Ras did not have such an effect, suggesting that K-Ras(G12D), but not N-Ras (G12D), activates the MEK-ERK signaling pathway and thereby promotes the proliferation of colonic epithelial cells [146,147]. Activated MEK1/2 has also been shown to up-regulate the expression of matrix metalloproteinases and to protect cancer cells from anoikis, or detachment-induced apoptosis [148].

Mutations in the B-Raf gene are responsible for ~66% of malignant melanomas [149]. The substitution of glutamate for valine at amino acid 600 (V600E) of B-Raf is the most common of these mutations and results in constitutive activation of B-Raf and the ERK signaling pathway [150]. Mutations of B-Raf that do not affect its kinase activity can also increase MEK-ERK signaling as a result of the formation of a heterodimer between the mutant B-Raf and Raf-1 [151]. Mutations of the Raf-1 gene are also found in acute myeloid leukemia [152].

The ERK signaling pathway plays a role in several steps of tumor development. The phosphorylation by ERK of proteins such as myosin light chain kinase, calpain, focal adhesion kinase, and paxillin [153] promotes cancer cell migration. The ERK pathway also induces the expression of matrix metalloproteinases and thereby promotes the degradation of extracellular matrix proteins and consequent tumor invasion [154]. Furthermore, ERK1/2 signaling regulates the activities and levels of Bcl-2 family proteins such as the pro-apoptotic protein BIM and the anti-apoptotic protein MCL-1, thereby promoting the survival of cancer cells [155]. ERK thus mediates phosphorylation of the transcription factor FOXO3A, which results in proteasome-dependent degradation of the phosphorylated FOXO3A [156] and consequent down-regulation of FOXO3A-dependent transcription of the BIM gene [157]. ERK also phosphorylates MCL-1 on threonine-163 in the PEST domain, resulting in stabilization of MCL-1 and promoting the survival of tumor cells. MCL-1 expression is increased in several types of cancer and is associated with poor prognosis and resistance to anticancer drugs [158]. The ERK signaling pathway is therefore considered a prominent therapeutic target for the development of chemotherapeutic drugs, with sorafenib, a Raf inhibitor, being one of the most efficient such drugs available [159].

Mutations in the epidermal growth factor receptor (EGFR), which activates the ERK pathway, occur frequently in the lung and colorectal cancers [160,161]. Abnormal activation of EGFR has been demonstrated in ~80% of cases of non-small cell lung cancer [162]. The most common mutation of EGFR is an in-frame deletion in the tyrosine kinase domain, which results in activation of downstream signaling such as that mediated by the PI3K-Akt and Raf-MEK-ERK pathways [163]. Gefitinib and erlotinib, both of which are inhibitors of the tyrosine kinase activity of EGFR, are used to block the proliferation of non-small cell lung cancer cells [164]. Components of signaling pathways activated by EGFR have also received great attention as potential targets for the development of new therapeutic drugs for lung cancer [165,166].

5. Conclusion

MAPK signaling pathways have been implicated in the pathogenesis of a variety of human disorders including cancer and neurodegenerative diseases such as AD, PD, and ALS. In AD, activation of MAPK cascades contributes to disease progression through regulation of neuronal apoptosis, β- and γ-secretase activity, and phosphorylation of APP and tau. Inhibitors for ERK1/2, MEK, or JNK, all of which contribute to the pathological hyperphosphorylation of tau, have been widely investigated as potential therapeutic drugs for AD [167,168]. Inhibitors of p38 MAPK are also considered as potential drugs for AD, given that the p38 pathway plays a key role in the $A\beta_{42}$-induced production of pro-inflammatory cytokines [169]. In addition, D-JNKI1, a peptide inhibitor of JNK1, has been shown to reduce the levels of mature and secreted forms of APP in cultured neurons [170]. The development of a single agent to treat the symptoms of PD is likely to prove difficult because of the genetic complexity of this disease [171]. MLK isoform-specific inhibitors such as CEP-5104 and CEP-6331 have been investigated in the mouse MPTP model of PD in an attempt to develop second-generation drugs based on the pan-MLK inhibitor CEP-1347 [172]. Aberrant expression and activation of p38 MAPK have been demonstrated in motor neurons and microglia of ALS patients. Several compounds including p38 inhibitors are under investigation as potential therapeutic agents against ALS [135]. The ERK signaling pathway plays a central role in several steps of cancer development, including cancer cell migration and the development of resistance to apoptosis, such as that mediated by phosphorylation and consequent stabilization of the anti-apoptotic protein MCL-1. Inhibitors of the ERK signaling pathway are thus good candidates for the development of anticancer agents [173].

MAPK signaling pathways are also associated with the pathogenesis of several other chronic and genetic diseases such as Crohn's disease, polycystic kidney disease, and the Ras-MAPK syndromes. A clinical trial of CNI-1493, a JNK and p38 inhibitor, revealed beneficial effects on ulcer healing in patients with Crohn's disease, a chronic inflammatory bowel condition [174]. Polycystic kidney disease actually comprises a large family of genetic diseases characterized by renal failure. The Ras-MAPK signaling pathway has been implicated in the pathogenesis of polycystic kidney disease in studies with transgenic mice expressing H-Ras [175]. Germline mutation of the H-Ras gene has also been identified in Costello syndrome. Furthermore, dysregulation of the Ras-MAPK signaling pathway has been identified as a principal cause of the Ras-MAPK syndromes, which include Noonan, LEOPARD, Costello, and cardio-facio-cutaneous syndromes as well as neurofibromatosis type I [176].

Given that the same components of MAPK signaling pathways act differentially in the pathogenic mechanisms of many human diseases, knowledge of the tissue- and disease-specific regulatory mechanisms for MAPK signaling pathways might provide clues for the development of new therapeutic drugs for human diseases.

Acknowledgements

This work was supported by the Korea Research Foundation Grant (KRF-2006-341-C00023), by the Basic Science Research Program (2009-0080895) through the National Research Foundation of Korea (NRF), and a NRF grant (20090081488) (E.-J.C.), and a NRF grant (2009-0067112) (E.K.K.) funded by the Ministry of Education, Science and Technology, South Korea.

References

[1] J.A. McCubrey, M.M. Lahair, R.A. Franklin, Reactive oxygen species-induced activation of the MAP kinase signaling pathways, Antioxid. Redox Signal. 8 (2006) 1775–1789.
[2] S. Torii, T. Yamamoto, Y. Tsuchiya, E. Nishida, ERK MAP kinase in G cell cycle progression and cancer, Cancer Sci. 97 (2006) 697–702.
[3] A.S. Dhillon, S. Hagan, O. Rath, W. Kolch, MAP kinase signalling pathways in cancer, Oncogene 26 (2007) 3279–3290.
[4] H.J. Schaeffer, M.J. Weber, Mitogen-activated protein kinases: specific messages from ubiquitous messengers, Mol. Cell. Biol. 19 (1999) 2435–2444.
[5] D.K. Morrison, R.J. Davis, Regulation of MAP kinase signaling modules by scaffold proteins in mammals, Annu. Rev. Cell Dev. Biol. 19 (2003) 91–118.
[6] A.J. Whitmarsh, The J.I.P. family of MAPK scaffold proteins, Biochem. Soc. Trans. 34 (2006) 828–832.

[7] R.J. Davis, Signal transduction by the JNK group of MAP kinases, Cell 103 (2000) 239–252.
[8] M. Malumbres, M. Barbacid, RAS oncogenes: the first 30 years, Nat. Rev. Cancer 3 (2003) 459–465.
[9] M.T. Uhlik, A.N. Abell, B.D. Cuevas, K. Nakamura, G.L. Johnson, Wiring diagrams of MAPK regulation by MEKK1, 2, and 3, Biochem. Cell Biol. 82 (2004) 658–663.
[10] B.D. Cuevas, A.M. Winter-Vann, N.L. Johnson, G.L. Johnson, MEKK1 controls matrix degradation and tumor cell dissemination during metastasis of polyoma middle-T driven mammary cancer, Oncogene 25 (2006) 4998–5010.
[11] H. Nagai, T. Noguchi, K. Takeda, H. Ichijo, Pathophysiological roles of ASK1-MAP kinase signaling pathways, J. Biochem. Mol. Biol. 40 (2007) 1–6.
[12] E. Giacobini, R.E. Becker, One hundred years after the discovery of Alzheimer's disease. A turning point for therapy? J. Alzheimers Dis. 12 (2007) 37–52.
[13] P.C. Reid, Y. Urano, T. Kodama, T. Hamakubo, Alzheimer's disease: cholesterol, membrane rafts, isoprenoids and statins, J. Cell. Mol. Med. 11 (2007) 383–392.
[14] M. Tabaton, E. Tamagno, The molecular link between β- and γ-secretase activity on the amyloid β precursor protein, Cell. Mol. Life Sci. 64 (2007) 2211–2218.
[15] J.Z. Wang, F. Liu, Microtubule-associated protein tau in development, degeneration and protection of neurons, Prog. Neurobiol. 85 (2008) 148–175.
[16] M. Perez, M.A. Moran, I. Ferrer, J. Avila, P. Gomez-Ramos, Phosphorylated tau in neuritic plaques of APP(sw)/Tau (vlw) transgenic mice and Alzheimer disease, Acta Neuropathol. 116 (2008) 409–418.
[17] J.B. Paulson, M. Ramsden, C. Forster, M.A. Sherman, E. McGowan, K.H. Ashe, Amyloid plaque and neurofibrillary tangle pathology in a regulatable mouse model of Alzheimer's disease, Am. J. Pathol. 173 (2008) 762–772.
[18] N.N. Dewji, The structure and functions of the presenilins, Cell. Mol. Life Sci. 62 (2005) 1109–1119.
[19] J.L. Jankowsky, D.J. Fadale, J. Anderson, G.M. Xu, V. Gonzales, N.A. Jenkins, N.G. Copeland, M.K. Lee, L.H. Younkin, S.L. Wagner, S.G. Younkin, D.R. Borchelt, Mutant presenilins specifically elevate the levels of the 42 residue β-amyloid peptide in vivo: evidence for augmentation of a 42-specific γ secretase, Hum. Mol. Genet. 13 (2004) 159–170.
[20] L. Placanica, L. Zhu, Y.M. Li, Gender- and age-dependent γ-secretase activity in mouse brain and its implication in sporadic Alzheimer disease, PLoS One 4 (2009) e5088.
[21] E. Kojro, F. Fahrenholz, The non-amyloidogenic pathway: structure and function of α-secretases, Subcell. Biochem. 38 (2005) 105–127.
[22] S. Sinha, J.P. Anderson, R. Barbour, G.S. Basi, R. Caccavello, D. Davis, M. Doan, H.F. Dovey, N. Frigon, J. Hong, K. Jacobson-Croak, N. Jewett, P. Keim, J. Knops, I. Lieberburg, M. Power, H. Tan, G. Tatsuno, J. Tung, D. Schenk, P. Seubert, S.M. Suomensaari, S. Wang, D. Walker, J. Zhao, L. McConlogue, V. John, Purification and cloning of amyloid precursor protein β-secretase from human brain, Nature 402 (1999) 537–540.
[23] G. Yu, M. Nishimura, S. Arawaka, D. Levitan, L. Zhang, A. Tandon, Y.Q. Song, E. Rogaeva, F. Chen, T. Kawarai, A. Supala, L. Levesque, H. Yu, D.S. Yang, E. Holmes, P. Milman, Y. Liang, D.M. Zhang, D.H. Xu, C. Sato, E. Rogaev, M. Smith, C. Janus, Y. Zhang, R. Aebersold, L.S. Farrer, S. Sorbi, A. Bruni, P. Fraser, P. St George-Hyslop, Nicastrin modulates presenilin-mediated *notch/glp-1* signal transduction and βAPP processing, Nature 407 (2000) 48–54.
[24] R. Vassar, B.D. Bennett, S. Babu-Khan, S. Kahn, E.A. Mendiaz, P. Denis, D.B. Teplow, S. Ross, P. Amarante, R. Loeloff, Y. Luo, S. Fisher, J. Fuller, S. Edenson, J. Lile, M.A. Jarosinski, A.L. Biere, E. Curran, T. Burgess, J.C. Louis, F. Collins, J. Treanor, G. Rogers, M. Citron, β-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE, Science 286 (1999) 735–741.
[25] F.M. LaFerla, K.N. Green, S. Oddo, Intracellular amyloid-β in Alzheimer's disease, Nat. Rev. Neurosci. 8 (2007) 499–509.
[26] C. Caspersen, N. Wang, J. Yao, A. Sosunov, X. Chen, J.W. Lustbader, H.W. Xu, D. Stern, G. McKhann, S.D. Yan, Mitochondrial Aβ: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease, FASEB J. 19 (2005) 2040–2041.
[27] S. Melov, P.A. Adlard, K. Morten, F. Johnson, T.R. Golden, D. Hinerfeld, B. Schilling, C. Mavros, C.L. Masters, I. Volitakis, Q.X. Li, K. Laughton, A. Hubbard, R.A. Cherny, B. Gibson, A.I. Bush, Mitochondrial oxidative stress causes hyperphosphorylation of tau, PLoS One 2 (2007) e536.
[28] M.T. Lin, M.F. Beal, Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases, Nature 443 (2006) 787–795.
[29] D. Pratico, Oxidative stress hypothesis in Alzheimer's disease: a reappraisal, Trends Pharmacol. Sci. 29 (2008) 609–615.
[30] X. Zhu, H.G. Lee, A.K. Raina, G. Perry, M.A. Smith, The role of mitogen-activated protein kinase pathways in Alzheimer's disease, Neurosignals 11 (2002) 270–281.
[31] B.J. Tabner, O.M. El-Agnaf, S. Turnbull, M.J. German, K.E. Paleologou, Y. Hayashi, L.J. Cooper, N.J. Fullwood, D. Allsop, Hydrogen peroxide is generated during the very early stages of aggregation of the amyloid peptides implicated in Alzheimer disease and familial British dementia, J. Biol. Chem. 280 (2005) 35789–35792.
[32] A. Chiarini, I. Dal Pra, M. Marconi, B. Chakravarthy, J.F. Whitfield, U. Armato, Calcium-sensing receptor (CaSR) in human brain's pathophysiology: roles in late-onset Alzheimer's disease (LOAD), Curr. Pharm. Biotechnol. 10 (2009) 317–326.
[33] B. Puig, T. Gomez-Isla, E. Ribe, M. Cuadrado, B. Torrejon-Escribano, E. Dalfo, I. Ferrer, Expression of stress-activated kinases c-Jun N-terminal kinase (SAPK/JNK-P) and p38 kinase (p38-P), and tau hyperphosphorylation in neurites surrounding βA plaques in APP Tg2576 mice, Neuropathol. Appl. Neurobiol. 30 (2004) 491–502.
[34] C.A. Marques, U. Keil, A. Bonert, B. Steiner, C. Haass, W.E. Muller, A. Eckert, Neurotoxic mechanisms caused by the Alzheimer's disease-linked Swedish amyloid precursor protein mutation: oxidative stress, caspases, and the JNK pathway, J. Biol. Chem. 278 (2003) 28294–28302.
[35] Y. Hashimoto, O. Tsuji, T. Niikura, Y. Yamagishi, M. Ishizaka, M. Kawasumi, T. Chiba, K. Kanekura, M. Yamada, E. Tsukamoto, K. Kouyama, K. Terashita, S. Aiso, A. Lin, I. Nishimoto, Involvement of c-Jun N-terminal kinase in amyloid precursor protein-mediated neuronal cell death, J. Neurochem. 84 (2003) 864–877.
[36] E. Tamagno, M. Parola, P. Bardini, A. Piccini, R. Borghi, M. Guglielmotto, G. Santoro, A. Davit, O. Danni, M.A. Smith, G. Perry, M. Tabaton, β-Site APP cleaving enzyme up-regulation induced by 4-hydroxynonenal is mediated by stress-activated protein kinases pathways, J. Neurochem. 92 (2005) 628–636.
[37] C. Shen, Y. Chen, H. Liu, K. Zhang, T. Zhang, A. Lin, N. Jing, Hydrogen peroxide promotes Aβ production through JNK-dependent activation of γ-secretase, J. Biol. Chem. 283 (2008) 17721–17730.
[38] A. Colombo, A. Bastone, C. Ploia, A. Sclip, M. Salmona, G. Forloni, T. Borsello, JNK regulates APP cleavage and degradation in a model of Alzheimer's disease, Neurobiol. Dis. 33 (2009) 518–525.
[39] Z. Muresan, V. Muresan, The amyloid-β precursor protein is phosphorylated via distinct pathways during differentiation, mitosis, stress, and degeneration, Mol. Biol. Cell 18 (2007) 3835–3844.
[40] Y. Sekine, K. Takeda, H. Ichijo, The ASK1-MAP kinase signaling in ER stress and neurodegenerative diseases, Curr. Mol. Med. 6 (2006) 87–97.
[41] A.L. Peel, N. Sorscher, J.Y. Kim, V. Galvan, S. Chen, D.E. Bredesen, Tau phosphorylation in Alzheimer's disease: potential involvement of an APP-MAP kinase complex, Neuromolecular Med. 5 (2004) 205–218.
[42] V. Galvan, S. Banwait, P. Spilman, O.F. Gorostiza, A. Peel, M. Ataie, D. Crippen, W. Huang, G. Sidhu, H. Ichijo, D.E. Bredesen, Interaction of ASK1 and the β-amyloid precursor protein in a stress-signaling complex, Neurobiol. Dis. 28 (2007) 65–75.
[43] M. Leyssen, D. Ayaz, S.S. Hebert, S. Reeve, B. De Strooper, B.A. Hassan, Amyloid precursor protein promotes post-developmental neurite arborization in the *Drosophila* brain, EMBO J. 24 (2005) 2944–2955.
[44] E. Tamagno, M. Guglielmotto, L. Giliberto, A. Vitali, R. Borghi, R. Autelli, O. Danni, M. Tabaton, JNK and ERK1/2 pathways have a dual opposite effect on the expression of BACE1, Neurobiol. Aging 30 (2009) 1563–1573.
[45] Y.F. Liao, B.J. Wang, H.T. Cheng, L.H. Kuo, M.S. Wolfe, Tumor necrosis factor-α interleukin-1β and interferon-γ stimulate γ-secretase-mediated cleavage of amyloid precursor protein through a JNK-dependent MAPK pathway, J. Biol. Chem. 279 (2004) 49523–49532.
[46] Y. Hashimoto, T. Chiba, M. Yamada, M. Nawa, K. Kanekura, H. Suzuki, K. Terashita, S. Aiso, I. Nishimoto, M. Matsuoka, Transforming growth factor β2 is a neuronal death-inducing ligand for amyloid-β precursor protein, Mol. Cell. Biol. 25 (2005) 9304–9317.
[47] S. Gandhi, N.W. Wood, Molecular pathogenesis of Parkinson's disease, Hum. Mol. Genet. 14 (2005) 2749–2755.
[48] W. Poewe, Non-motor symptoms in Parkinson's disease, Eur. J. Neurol. 15 (1) (2008) 14–20.
[49] S. Lesage, A. Brice, Parkinson's disease: from monogenic forms to genetic susceptibility factors, Hum. Mol. Genet. 18 (2009) R48–R59.
[50] M.G. Spillantini, M.L. Schmidt, V.M. Lee, J.Q. Trojanowski, R. Jakes, M. Goedert, α-synuclein in Lewy bodies, Nature 388 (1997) 839–840.
[51] A. Abeliovich, Y. Schmitz, I. Farinas, D. Choi-Lundberg, W.H. Ho, P.E. Castillo, N. Shinsky, J.M. Verdugo, M. Armanini, A. Ryan, M. Hynes, H. Phillips, D. Sulzer, A. Rosenthal, Mice lacking α-synuclein display functional deficits in the nigrostriatal dopamine system, Neuron 25 (2000) 239–252.
[52] M.H. Polymeropoulos, C. Lavedan, E. Leroy, S.E. Ide, A. Dehejia, A. Dutra, B. Pike, H. Root, J. Rubenstein, R. Boyer, E.S. Stenroos, S. Chandrasekharappa, A. Athanassiadou, T. Papapetropoulos, W.G. Johnson, A.M. Lazzarini, R.C. Duvoisin, G. Di Iorio, L.I. Golbe, R.L. Nussbaum, Mutation in the α-synuclein gene identified in families with Parkinson's disease, Science 276 (1997) 2045–2047.
[53] A.B. Singleton, M. Farrer, J. Johnson, A. Singleton, S. Hague, J. Kachergus, M. Hulihan, T. Peuralinna, A. Dutra, R. Nussbaum, S. Lincoln, A. Crawley, M. Hanson, D. Maraganore, C. Adler, M.R. Cookson, M. Muenter, M. Baptista, D. Miller, J. Blancato, J. Hardy, K. Gwinn-Hardy, α-Synuclein locus triplication causes Parkinson's disease, Science 302 (2003) 841.
[54] M.C. Chartier-Harlin, J. Kachergus, C. Roumier, V. Mouroux, X. Douay, S. Lincoln, C. Levecque, L. Larvor, J. Andrieux, M. Hulihan, N. Waucquier, L. Defebvre, P. Amouyel, M. Farrer, A. Destee, α-Synuclein locus duplication as a cause of familial Parkinson's disease, Lancet 364 (2004) 1167–1169.
[55] L. Chen, M.B. Feany, α-Synuclein phosphorylation controls neurotoxicity and inclusion formation in a *Drosophila* model of Parkinson disease, Nat. Neurosci. 8 (2005) 657–663.
[56] K.J. Inglis, D. Chereau, E.F. Brigham, S.S. Chiou, S. Schobel, N.L. Frigon, M. Yu, R.J. Caccavello, S. Nelson, R. Motter, S. Wright, D. Chian, P. Santiago, F. Soriano, C. Ramos, K. Powell, J.M. Goldstein, M. Babcock, T. Yednock, F. Bard, G.S. Basi, H. Sham, T.J. Chilcote, L. McConlogue, I. Griswold-Prenner, J.P. Anderson, Polo-like kinase 2 (PLK2) phosphorylates α-synuclein at serine 129 in central nervous system, J. Biol. Chem. 284 (2009) 2598–2602.
[57] G.K. Tofaris, A. Razzaq, B. Ghetti, K.S. Lilley, M.G. Spillantini, Ubiquitination of α-synuclein in Lewy bodies is a pathological event not associated with impairment of proteasome function, J. Biol. Chem. 278 (2003) 44405–44411.
[58] B.I. Giasson, J.E. Duda, I.V. Murray, Q. Chen, J.M. Souza, H.I. Hurtig, H. Ischiropoulos, J.Q. Trojanowski, V.M. Lee, Oxidative damage linked to neurodegeneration by selective α-synuclein nitration in synucleinopathy lesions, Science 290 (2000) 985–989.
[59] G.K. Tofaris, P. Garcia Reitbock, T. Humby, S.L. Lambourne, M. O'Connell, B. Ghetti, H. Gossage, P.C. Emson, L.S. Wilkinson, M. Goedert, M.G. Spillantini, Pathological changes in dopaminergic nerve cells of the substantia nigra and

olfactory bulb in mice transgenic for truncated human α-synuclein(1–120): implications for Lewy body disorders, J. Neurosci. 26 (2006) 3942–3950.
[60] M.R. Cookson, α-Synuclein and neuronal cell death, Mol. Neurodegener. 4 (2009) 9.
[61] A.R. Saha, N.N. Ninkina, D.P. Hanger, B.H. Anderton, A.M. Davies, V.L. Buchman, Induction of neuronal death by α-synuclein, Eur. J. Neurosci. 12 (2000) 3073–3077.
[62] E.C. Hirsch, S. Hunot, Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 8 (2009) 382–397.
[63] O.A. Levy, C. Malagelada, L.A. Greene, Cell death pathways in Parkinson's disease: proximal triggers, distal effectors, and final steps, Apoptosis 14 (2009) 478–500.
[64] R.L. Miller, M. James-Kracke, G.Y. Sun, A.Y. Sun, Oxidative and inflammatory pathways in Parkinson's disease, Neurochem. Res. 34 (2009) 55–65.
[65] G.E. Meredith, P.K. Sonsalla, M.F. Chesselet, Animal models of Parkinson's disease progression, Acta Neuropathol. 115 (2008) 385–398.
[66] W. Zhang, T. Wang, Z. Pei, D.S. Miller, X. Wu, M.L. Block, B. Wilson, W. Zhang, Y. Zhou, J.S. Hong, J. Zhang, Aggregated α-synuclein activates microglia: a process leading to disease progression in Parkinson's disease, FASEB J. 19 (2005) 533–542.
[67] A. Klegeris, S. Pelech, B.I. Giasson, J. Maguire, H. Zhang, E.G. McGeer, P.L. McGeer, α-Synuclein activates stress signaling protein kinases in THP-1 cells and microglia, Neurobiol. Aging 29 (2008) 739–752.
[68] A. Klegeris, B.I. Giasson, H. Zhang, J. Maguire, S. Pelech, P.L. McGeer, α-Synuclein and its disease-causing mutants induce ICAM-1 and IL-6 in human astrocytes and astrocytoma cells, FASEB J. 20 (2006) 2000–2008.
[69] L. Devi, V. Raghavendran, B.M. Prabhu, N.G. Avadhani, H.K. Anandatheerthavarada, Mitochondrial import and accumulation of α-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain, J. Biol. Chem. 283 (2008) 9089–9100.
[70] M.S. Parihar, A. Parihar, M. Fujita, M. Hashimoto, P. Ghafourifar, Mitochondrial association of α-synuclein causes oxidative stress, Cell. Mol. Life Sci. 65 (2008) 1272–1284.
[71] A. Schober, Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP, Cell Tissue Res. 318 (2004) 215–224.
[72] F. Cicchetti, J. Drouin-Ouellet, R.E. Gross, Environmental toxins and Parkinson's disease: what have we learned from pesticide-induced animal models? Trends Pharmacol. Sci. 30 (2009) 475–483.
[73] D. Adam, Pesticide use linked to Parkinson's disease, Nature 408 (2000) 125.
[74] J.M. Hatcher, K.D. Pennell, G.W. Miller, Parkinson's disease and pesticides: a toxicological perspective, Trends Pharmacol. Sci. 29 (2008) 322–329.
[75] M.F. Beal, Experimental models of Parkinson's disease, Nat. Rev. Neurosci. 2 (2001) 325–334.
[76] S. Karunakaran, L. Diwakar, U. Saeed, V. Agarwal, S. Ramakrishnan, S. Iyengar, V. Ravindranath, Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of death-associated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: protection by α-lipoic acid, FASEB J. 21 (2007) 2226–2236.
[77] M.S. Saporito, B.A. Thomas, R.W. Scott, MPTP activates c-Jun NH(2)-terminal kinase (JNK) and its upstream regulatory kinase MKK4 in nigrostriatal neurons in vivo, J. Neurochem. 75 (2000) 1200–1208.
[78] M. Ouyang, X. Shen, Critical role of ASK1 in the 6-hydroxydopamine-induced apoptosis in human neuroblastoma SH-SY5Y cells, J. Neurochem. 97 (2006) 234–244.
[79] R.M. Silva, C.Y. Kuan, P. Rakic, R.E. Burke, Mixed lineage kinase-c-jun N-terminal kinase signaling pathway: a new therapeutic target in Parkinson's disease, Mov. Disord. 20 (2005) 653–664.
[80] J.R. Mathiasen, B.A. McKenna, M.S. Saporito, G.D. Ghadge, R.P. Roos, B.P. Holskin, Z.L. Wu, S.P. Trusko, T.C. Connors, A.C. Maroney, B.A. Thomas, J.C. Thomas, D. Bozyczko-Coyne, Inhibition of mixed lineage kinase 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells, Brain Res. 1003 (2004) 86–97.
[81] J.E. Chipuk, D.R. Green, How do BCL-2 proteins induce mitochondrial outer membrane permeabilization? Trends Cell Biol. 18 (2008) 157–164.
[82] S. Karunakaran, U. Saeed, M. Mishra, R.K. Valli, S.D. Joshi, D.P. Meka, P. Seth, V. Ravindranath, Selective activation of p38 mitogen-activated protein kinase in dopaminergic neurons of substantia nigra leads to nuclear translocation of p53 in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-treated mice, J. Neurosci. 28 (2008) 12500–12509.
[83] N. Rawal, C. Parish, G. Castelo-Branco, E. Arenas, Inhibition of JNK increases survival of transplanted dopamine neurons in Parkinsonian rats, Cell Death Differ. 14 (2007) 381–383.
[84] J. Pan, Y.X. Zhao, Z.Q. Wang, L. Jin, Z.K. Sun, S.D. Chen, Expression of FasL and its interaction with Fas are mediated by c-Jun N-terminal kinase (JNK) pathway in 6-OHDA-induced rat model of Parkinson disease, Neurosci. Lett. 428 (2007) 82–87.
[85] K. Newhouse, S.L. Hsuan, S.H. Chang, B. Cai, Y. Wang, Z. Xia, Rotenone-induced apoptosis is mediated by p38 and JNK MAP kinases in human dopaminergic SH-SY5Y cells, Toxicol. Sci. 79 (2004) 137–146.
[86] S.L. Hsuan, H.M. Klintworth, Z. Xia, Basic fibroblast growth factor protects against rotenone-induced dopaminergic cell death through activation of extracellular signal-regulated kinases 1/2 and phosphatidylinositol-3 kinase pathways, J. Neurosci. 26 (2006) 4481–4491.
[87] J. Peng, X.O. Mao, F.F. Stevenson, M. Hsu, J.K. Andersen, The herbicide paraquat induces dopaminergic nigral apoptosis through sustained activation of the JNK pathway, J. Biol. Chem. 279 (2004) 32626–32632.
[88] H. Klintworth, K. Newhouse, T. Li, W.S. Choi, R. Faigle, Z. Xia, Activation of c-Jun N-terminal protein kinase is a common mechanism underlying paraquat- and rotenone-induced dopaminergic cell apoptosis, Toxicol. Sci. 97 (2007) 149–162.
[89] S. Ramachandiran, J.M. Hansen, D.P. Jones, J.R. Richardson, G.W. Miller, Divergent mechanisms of paraquat, MPP+, and rotenone toxicity: oxidation of thioredoxin and caspase-3 activation, Toxicol. Sci. 95 (2007) 163–171.
[90] L. Resnick, M. Fennell, Targeting JNK3 for the treatment of neurodegenerative disorders, Drug Discov. Today 9 (2004) 932–939.
[91] M.S. Saporito, R.L. Hudkins, A.C. Maroney, Discovery of CEP-1347/KT-7515, an inhibitor of the JNK/SAPK pathway for the treatment of neurodegenerative diseases, Prog. Med. Chem. 40 (2002) 23–62.
[92] Parkinson study group PRECEP investigators, Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease, Neurology 69 (2007) 1480–1490.
[93] C.Y. Kuan, R.E. Burke, Targeting the JNK signaling pathway for stroke and Parkinson's diseases therapy, Curr. Drug Targets. CNS Neurol. Disord. 4 (2005) 63–67.
[94] L. Guo, W. Wang, S.G. Chen, Leucine-rich repeat kinase 2: relevance to Parkinson's disease, Int. J. Biochem. Cell Biol. 38 (2006) 1469–1475.
[95] A. Zimprich, S. Biskup, P. Leitner, P. Lichtner, M. Farrer, S. Lincoln, J. Kachergus, M. Hulihan, R.J. Uitti, D.B. Calne, A.J. Stoessl, R.F. Pfeiffer, N. Patenge, I.C. Carbajal, P. Vieregge, F. Asmus, B. Muller-Myhsok, D.W. Dickson, T. Meitinger, T.M. Strom, Z.K. Wszolek, T. Gasser, Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology, Neuron 44 (2004) 601–607.
[96] A.B. West, D.J. Moore, S. Biskup, A. Bugayenko, W.W. Smith, C.A. Ross, V.L. Dawson, T.M. Dawson, Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 16842–16847.
[97] L.R. White, M. Toft, S.N. Kvam, M.J. Farrer, J.O. Aasly, MAPK-pathway activity, Lrrk2 G2019S, and Parkinson's disease, J. Neurosci. Res. 85 (2007) 1288–1294.
[98] C.J. Gloeckner, A. Schumacher, K. Boldt, M. Ueffing, The Parkinson disease-associated protein kinase LRRK2 exhibits MAPKKK activity and phosphorylates MKK3/6 and MKK4/7, in vitro, J. Neurochem. 109 (2009) 959–968.
[99] S.S. Safadi, G.S. Shaw, A disease state mutation unfolds the parkin ubiquitin-like domain, Biochemistry 46 (2007) 14162–14169.
[100] J.F. Staropoli, C. McDermott, C. Martinat, B. Schulman, E. Demireva, A. Abeliovich, Parkin is a component of an SCF-like ubiquitin ligase complex and protects postmitotic neurons from kainate excitotoxicity, Neuron 37 (2003) 735–749.
[101] K.K. Chung, Y. Zhang, K.L. Lim, Y. Tanaka, H. Huang, J. Gao, C.A. Ross, V.L. Dawson, T.M. Dawson, Parkin ubiquitinates the α-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease, Nat. Med. 7 (2001) 1144–1150.
[102] M.K. Lim, T. Kawamura, Y. Ohsawa, M. Ohtsubo, S. Asakawa, A. Takayanagi, N. Shimizu, Parkin interacts with LIM Kinase 1 and reduces its cofilin-phosphorylation activity via ubiquitination, Exp. Cell Res. 313 (2007) 2858–2874.
[103] L. Petrucelli, C. O'Farrell, P.J. Lockhart, M. Baptista, K. Kehoe, L. Vink, P. Choi, B. Wolozin, M. Farrer, J. Hardy, M.R. Cookson, Parkin protects against the toxicity associated with mutant α-synuclein: proteasome dysfunction selectively affects catecholaminergic neurons, Neuron 36 (2002) 1007–1019.
[104] H. Jiang, Y. Ren, J. Zhao, J. Feng, Parkin protects human dopaminergic neuroblastoma cells against dopamine-induced apoptosis, Hum. Mol. Genet. 13 (2004) 1745–1754.
[105] G.H. Cha, S. Kim, J. Park, E. Lee, M. Kim, S.B. Lee, J.M. Kim, J. Chung, K.S. Cho, Parkin negatively regulates JNK pathway in the dopaminergic neurons of *Drosophila*, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 10345–10350.
[106] D. Narendra, A. Tanaka, D.F. Suen, R.J. Youle, Parkin is recruited selectively to impaired mitochondria and promotes their autophagy, J. Cell Biol. 183 (2008) 795–803.
[107] H.M. McBride, Parkin mitochondria in the autophagosome, J. Cell Biol. 183 (2008) 757–759.
[108] R. Cesari, E.S. Martin, G.A. Calin, F. Pentimalli, R. Bichi, H. McAdams, F. Trapasso, A. Drusco, M. Shimizu, V. Masciullo, G. D'Andrilli, G. Scambia, M.C. Picchio, H. Alder, A.K. Godwin, C.M. Croce, Parkin, a gene implicated in autosomal recessive juvenile parkinsonism, is a candidate tumor suppressor gene on chromosome 6q25-q27, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 5956–5961.
[109] J.F. Staropoli, Tumorigenesis and neurodegeneration: two sides of the same coin? Bioessays 30 (2008) 719–727.
[110] H. Xiong, D. Wang, L. Chen, Y.S. Choo, H. Ma, C. Tang, K. Xia, W. Jiang, Z. Ronai, X. Zhuang, Z. Zhang, Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation, J. Clin. Invest. 119 (2009) 650–660.
[111] R.D. Mills, C.H. Sim, S.S. Mok, T.D. Mulhern, J.G. Culvenor, H.C. Cheng, Biochemical aspects of the neuroprotective mechanism of PTEN-induced kinase-1 (PINK1), J. Neurochem. 105 (2008) 18–33.
[112] J. Park, S.B. Lee, S. Lee, Y. Kim, S. Song, S. Kim, E. Bae, J. Kim, M. Shong, J.M. Kim, J. Chung, Mitochondrial dysfunction in *Drosophila* PINK1 mutants is complemented by parkin, Nature 441 (2006) 1157–1161.
[113] E. Andres-Mateos, C. Perier, L. Zhang, B. Blanchard-Fillion, T.M. Greco, B. Thomas, H.S. Ko, M. Sasaki, H. Ischiropoulos, S. Przedborski, T.M. Dawson, V.L. Dawson, DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 14807–14812.
[114] J. Xu, N. Zhong, H. Wang, J.E. Elias, C.Y. Kim, I. Woldman, C. Pifl, S.P. Gygi, C. Geula, B.A. Yankner, The Parkinson's disease-associated DJ-1 protein is a transcriptional co-activator that protects against neuronal apoptosis, Hum. Mol. Genet. 14 (2005) 1231–1241.
[115] E. Junn, W.H. Jang, X. Zhao, B.S. Jeong, M.M. Mouradian, Mitochondrial localization of DJ-1 leads to enhanced neuroprotection, J. Neurosci. Res. 87 (2009) 123–129.
[116] S. Batelli, D. Albani, R. Rametta, L. Polito, F. Prato, M. Pesaresi, A. Negro, G. Forloni, DJ-1 modulates α-synuclein aggregation state in a cellular model of oxidative

stress: relevance for Parkinson's disease and involvement of HSP70, PLoS One 3 (2008) e1884.
[117] J. Waak, S.S. Weber, A. Waldenmaier, K. Gorner, M. Alunni-Fabbroni, H. Schell, D. Vogt-Weisenhorn, T.T. Pham, V. Reumers, V. Baekelandt, W. Wurst, P.J. Kahle, Regulation of astrocyte inflammatory responses by the Parkinson's disease-associated gene DJ-1, FASEB J. 23 (2009) 2478–2489.
[118] J.S. Mo, M.Y. Kim, E.J. Ann, J.A. Hong, H.S. Park, DJ-1 modulates UV-induced oxidative stress signaling through the suppression of MEKK1 and cell death, Cell Death Differ. 15 (2008) 1030–1041.
[119] S. Zucchelli, S. Vilotti, R. Calligaris, Z.S. Lavina, M. Biagioli, R. Foti, L. De Maso, M. Pinto, M. Gorza, E. Speretta, C. Casseler, G. Tell, G. Del Sal, S. Gustincich, Aggresome-forming TTRAP mediates pro-apoptotic properties of Parkinson's disease-associated DJ-1 missense mutations, Cell Death Differ. 16 (2009) 428–438.
[120] L. Vande Walle, M. Lamkanfi, P. Vandenabeele, The mitochondrial serine protease HtrA2/Omi: an overview, Cell Death Differ. 15 (2008) 453–460.
[121] L.M. Martins, A. Morrison, K. Klupsch, V. Fedele, N. Moisoi, P. Teismann, A. Abuin, E. Grau, M. Geppert, G.P. Livi, C.L. Creasy, A. Martin, I. Hargreaves, S.J. Heales, H. Okada, S. Brandner, J.B. Schulz, T. Mak, J. Downward, Neuroprotective role of the Reaper-related serine protease HtrA2/Omi revealed by targeted deletion in mice, Mol. Cell. Biol. 24 (2004) 9848–9862.
[122] K.M. Strauss, L.M. Martins, H. Plun-Favreau, F.P. Marx, S. Kautzmann, D. Berg, T. Gasser, Z. Wszolek, T. Muller, A. Bornemann, H. Wolburg, J. Downward, O. Riess, J.B. Schulz, R. Kruger, Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease, Hum. Mol. Genet. 14 (2005) 2099–2111.
[123] J. Yun, J.H. Cao, M.W. Dodson, I.E. Clark, P. Kapahi, R.B. Chowdhury, M. Guo, Loss-of-function analysis suggests that Omi/HtrA2 is not an essential component of the PINK1/PARKIN pathway in vivo, J. Neurosci. 28 (2008) 14500–14510.
[124] H. Plun-Favreau, K. Klupsch, N. Moisoi, S. Gandhi, S. Kjaer, D. Frith, K. Harvey, E. Deas, R.J. Harvey, N. McDonald, N.W. Wood, L.M. Martins, J. Downward, The mitochondrial protease HtrA2 is regulated by Parkinson's disease-associated kinase PINK1, Nat. Cell Biol. 9 (2007) 1243–1252.
[125] P. Pasinelli, R.H. Brown, Molecular biology of amyotrophic lateral sclerosis: insights from genetics, Nat. Rev. Neurosci. 7 (2006) 710–723.
[126] S. Vucic, M.C. Kierna, Pathophysiology of neurodegeneration in familial amyotrophic lateral sclerosis, Curr. Mol. Med. 9 (2009) 255–272.
[127] I.R. Mackenzie, E.H. Bigio, P.G. Ince, F. Geser, M. Neumann, N.J. Cairns, L.K. Kwong, M.S. Forman, J. Ravits, H. Stewart, A. Eisen, L. McClusky, H.A. Kretzschmar, C.M. Monoranu, J.R. Highley, J. Kirby, T. Siddique, P.J. Shaw, V.M. Lee, J.Q. Trojanowski, Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations, Ann. Neurol. 61 (2007) 427–434.
[128] T.J. Kwiatkowski Jr., D.A. Bosco, A.L. Leclerc, E. Tamrazian, C.R. Vanderburg, C. Russ, A. Davis, J. Gilchrist, E.J. Kasarskis, T. Munsat, P. Valdmanis, G.A. Rouleau, B.A. Hosler, P. Cortelli, P.J. de Jong, Y. Yoshinaga, J.L. Haines, M.A. Pericak-Vance, J. Yan, N. Ticozzi, T. Siddique, D. McKenna-Yasek, P.C. Sapp, H.R. Horvitz, J.E. Landers, R.H. Brown Jr., Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis, Science 323 (2009) 1205–1208.
[129] C. Lagier-Tourenne, D.W. Cleveland, Rethinking ALS: the FUS about TDP-43, Cell 136 (2009) 1001–1004.
[130] P.J. Shaw, Molecular and cellular pathways of neurodegeneration in motor neurone disease, J. Neurol. Neurosurg. Psychiatry 76 (2005) 1046–1057.
[131] M.E. Gurney, H. Pu, A.Y. Chiu, M.C. Dal Canto, C.Y. Polchow, D.D. Alexander, J. Caliendo, A. Hentati, Y.W. Kwon, H.X. Deng, et al., Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation, Science 264 (1994) 1772–1775.
[132] C. Bendotti, M. Bao Cutrona, C. Cheroni, G. Grignaschi, D. Lo Coco, M. Peviani, M. Tortarolo, P. Veglianese, E. Zennaro, Inter- and intracellular signaling in amyotrophic lateral sclerosis: role of p38 mitogen-activated protein kinase, Neurodegener. Dis. 2 (2005) 128–134.
[133] M. Tortarolo, P. Veglianese, N. Calvaresi, A. Botturi, C. Rossi, A. Giorgini, A. Migheli, C. Bendotti, Persistent activation of p38 mitogen-activated protein kinase in a mouse model of familial amyotrophic lateral sclerosis correlates with disease progression, Mol. Cell. Neurosci. 23 (2003) 180–192.
[134] S.S. Holasek, T.M. Wengenack, K.K. Kandimalla, C. Montano, D.M. Gregor, G.L. Curran, J.F. Poduslo, Activation of the stress-activated MAP kinase, p38, but not JNK in cortical motor neurons during early presymptomatic stages of amyotrophic lateral sclerosis in transgenic mice, Brain Res. 1045 (2005) 185–198.
[135] M. Dewil, V.F. dela Cruz, L. Van Den Bosch, W. Robberecht, Inhibition of p38 mitogen activated protein kinase activation and mutant SOD1(G93A)-induced motor neuron death, Neurobiol. Dis. 26 (2007) 332–341.
[136] C. Bendotti, C. Atzori, R. Piva, M. Tortarolo, M.J. Strong, S. DeBiasi, A. Migheli, Activated p38MAPK is a novel component of the intracellular inclusions found in human amyotrophic lateral sclerosis and mutant SOD1 transgenic mice, J. Neuropathol. Exp. Neurol. 63 (2004) 113–119.
[137] S. Ackerley, A.J. Grierson, S. Banner, M.S. Perkinton, J. Brownlees, H.L. Byers, M. Ward, P. Thornhill, K. Hussain, J.S. Waby, B.H. Anderton, J.D. Cooper, C. Dingwall, P.N. Leigh, C.E. Shaw, C.C. Miller, p38α stress-activated protein kinase phosphorylates neurofilaments and is associated with neurofilament pathology in amyotrophic lateral sclerosis, Mol. Cell. Neurosci. 26 (2004) 354–364.
[138] J. Brownlees, A. Yates, N.P. Bajaj, D. Davis, B.H. Anderton, P.N. Leigh, C.E. Shaw, C.C. Miller, Phosphorylation of neurofilament heavy chain side-arms by stress activated protein kinase-1b/Jun N-terminal kinase-3, J. Cell Sci. 113 (2000) 401–407.
[139] C. Raoul, A.G. Estevez, H. Nishimune, D.W. Cleveland, O. deLapeyriere, C.E. Henderson, G. Haase, B. Pettmann, Motoneuron death triggered by a specific pathway downstream of Fas. Potentiation by ALS-linked SOD1 mutations, Neuron 35 (2002) 1067–1083.
[140] C. Raoul, E. Buhler, C. Sadeghi, A. Jacquier, P. Aebischer, B. Pettmann, C.E. Henderson, G. Haase, Chronic activation in presymptomatic amyotrophic lateral sclerosis (ALS) mice of a feedback loop involving Fas, Daxx, and FasL, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 6007–6012.
[141] B. Meusser, C. Hirsch, E. Jarosch, T. Sommer, ERAD: the long road to destruction, Nat. Cell Biol. 7 (2005) 766–772.
[142] H. Nishitoh, H. Kadowaki, A. Nagai, T. Maruyama, T. Yokota, H. Fukutomi, T. Noguchi, A. Matsuzawa, K. Takeda, H. Ichijo, ALS-linked mutant SOD1 induces ER stress- and ASK1-dependent motor neuron death by targeting Derlin-1, Genes Dev. 22 (2008) 1451–1464.
[143] H. Nishitoh, A. Matsuzawa, K. Tobiume, K. Saegusa, K. Takeda, K. Inoue, S. Hori, A. Kakizuka, H. Ichijo, ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats, Genes Dev. 16 (2002) 1345–1355.
[144] T. Boutros, E. Chevet, P. Metrakos, Mitogen-activated protein (MAP) kinase/MAP kinase phosphatase regulation: roles in cell growth, death, and cancer, Pharmacol. Rev. 60 (2008) 261–310.
[145] S. Schubbert, K. Shannon, G. Bollag, Hyperactive Ras in developmental disorders and cancer, Nat. Rev. Cancer 7 (2007) 295–308.
[146] K.M. Haigis, K.R. Kendall, Y. Wang, A. Cheung, M.C. Haigis, J.N. Glickman, M. Niwa-Kawakita, A. Sweet-Cordero, J. Sebolt-Leopold, K.M. Shannon, J. Settleman, M. Giovannini, T. Jacks, Differential effects of oncogenic K-Ras and N-Ras on proliferation, differentiation and tumor progression in the colon, Nat. Genet. 40 (2008) 600–608.
[147] S.R. Calcagno, S. Li, M. Colon, P.A. Kreinest, E.A. Thompson, A.P. Fields, N.R. Murray, Oncogenic K-ras promotes early carcinogenesis in the mouse proximal colon, Int. J. Cancer 122 (2008) 2462–2470.
[148] L. Voisin, C. Julien, S. Duhamel, K. Gopalbhai, I. Claveau, M.K. Saba-El-Leil, I.G. Rodrigue-Gervais, L. Gaboury, D. Lamarre, M. Basik, S. Meloche, Activation of MEK1 or MEK2 isoform is sufficient to fully transform intestinal epithelial cells and induce the formation of metastatic tumors, BMC Cancer 8 (2008) 337.
[149] E. Halilovic, D.B. Solit, Therapeutic strategies for inhibiting oncogenic BRAF signaling, Curr. Opin. Pharmacol. 8 (2008) 419–426.
[150] P.T. Wan, M.J. Garnett, S.M. Roe, S. Lee, D. Niculescu-Duvaz, V.M. Good, C.M. Jones, C.J. Marshall, C.J. Springer, D. Barford, R. Marais, Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF, Cell 116 (2004) 855–867.
[151] L.K. Rushworth, A.D. Hindley, E. O'Neill, W. Kolch, Regulation and role of Raf-1/B-Raf heterodimerization, Mol. Cell. Biol. 26 (2006) 2262–2272.
[152] A. Zebisch, P.B. Staber, A. Delavar, C. Bodner, K. Hiden, K. Fischereder, M. Janakiraman, W. Linkesch, H.W. Auner, W. Emberger, C. Windpassinger, M.G. Schimek, G. Hoefler, J. Troppmair, H. Sill, Two transforming C-RAF germ-line mutations identified in patients with therapy-related acute myeloid leukemia, Cancer Res. 66 (2006) 3401–3408.
[153] C. Huang, K. Jacobson, M.D. Schaller, MAP kinases and cell migration, J. Cell Sci. 117 (2004) 4619–4628.
[154] S. Chakraborti, M. Mandal, S. Das, A. Mandal, T. Chakraborti, Regulation of matrix metalloproteinases: an overview, Mol. Cell. Biochem. 253 (2003) 269–285.
[155] K. Balmanno, S.J. Cook, Tumour cell survival signalling by the ERK1/2 pathway, Cell Death Differ. 16 (2009) 368–377.
[156] R. Ley, K. Balmanno, K. Hadfield, C. Weston, S.J. Cook, Activation of the ERK1/2 signaling pathway promotes phosphorylation and proteasome-dependent degradation of the BH3-only protein, Bim, J. Biol. Chem. 278 (2003) 18811–18816.
[157] Z. Fu, D.J. Tindall, FOXOs, cancer and regulation of apoptosis, Oncogene 27 (2008) 2312–2319.
[158] M.R. Warr, G.C. Shore, Unique biology of Mcl-1: therapeutic opportunities in cancer, Curr. Mol. Med. 8 (2008) 138–147.
[159] M. Chaparro, L. Gonzalez Moreno, M. Trapero-Marugan, J. Medina, R. Moreno-Otero, Review article: pharmacological therapy for hepatocellular carcinoma with sorafenib and other oral agents, Aliment. Pharmacol. Ther. 28 (2008) 1269–1277.
[160] N.E. Hynes, G. MacDonald, ErbB receptors and signaling pathways in cancer, Curr. Opin. Cell Biol. 21 (2009) 177–184.
[161] H. Nagahara, K. Mimori, M. Ohta, T. Utsunomiya, H. Inoue, G.F. Barnard, M. Ohira, K. Hirakawa, M. Mori, Somatic mutations of epidermal growth factor receptor in colorectal carcinoma, Clin. Cancer Res. 11 (2005) 1368–1371.
[162] G.K. Dy, A.A. Adjei, Emerging therapeutic targets in non-small cell lung cancer, Proc. Am. Thorac. Soc. 6 (2009) 218–223.
[163] J.G. Paez, P.A. Janne, J.C. Lee, S. Tracy, H. Greulich, S. Gabriel, P. Herman, F.J. Kaye, N. Lindeman, T.J. Boggon, K. Naoki, H. Sasaki, Y. Fujii, M.J. Eck, W.R. Sellers, B.E. Johnson, M. Meyerson, EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy, Science 304 (2004) 1497–1500.
[164] J.Q. Zhu, W.Z. Zhong, G.C. Zhang, R. Li, X.C. Zhang, A.L. Guo, Y.F. Zhang, S.J. An, T.S. Mok, Y.L. Wu, Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals, Cancer Lett. 265 (2008) 307–317.
[165] J.A. Engelman, L. Chen, X. Tan, K. Crosby, A.R. Guimaraes, R. Upadhyay, M. Maira, K. McNamara, S.A. Perera, Y. Song, L.R. Chirieac, R. Kaur, A. Lightbown, J. Simendinger, T. Li, R.F. Padera, C. Garcia-Echeverria, R. Weissleder, U. Mahmood, L.C. Cantley, K.K. Wong, Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers, Nat. Med. 14 (2008) 1351–1356.
[166] J. Downward, Targeting RAS and PI3K in lung cancer, Nat. Med. 14 (2008) 1315–1316.
[167] M.A. Bogoyevitch, I. Boehm, A. Oakley, A.J. Ketterman, R.K. Barr, Targeting the JNK MAPK cascade for inhibition: basic science and therapeutic potential, Biochim. Biophys. Acta 1697 (2004) 89–101.

[168] I. Churcher, Tau therapeutic strategies for the treatment of Alzheimer's disease, Curr. Top. Med. Chem. 6 (2006) 579–595.
[169] L. Munoz, H.R. Ranaivo, S.M. Roy, W. Hu, J.M. Craft, L.K. McNamara, L.W. Chico, L.J. Van Eldik, D.M. Watterson, A novel p38α MAPK inhibitor suppresses brain proinflammatory cytokine up-regulation and attenuates synaptic dysfunction and behavioral deficits in an Alzheimer's disease mouse model, J. Neuroinflammation 4 (2007) 21.
[170] A. Colombo, M. Repici, M. Pesaresi, S. Santambrogio, G. Forloni, T. Borsello, The TAT-JNK inhibitor peptide interferes with β amyloid protein stability, Cell Death Differ. 14 (2007) 1845–1848.
[171] C.W. Olanow, K. Kieburtz, A.H. Schapira, Why have we failed to achieve neuroprotection in Parkinson's disease? Ann. Neurol. 64 (2) (2008) S101–S110.
[172] R.L. Hudkins, J.L. Diebold, M. Tao, K.A. Josef, C.H. Park, T.S. Angeles, L.D. Aimone, J. Husten, M.A. Ator, S.L. Meyer, B.P. Holskin, J.T. Durkin, A.A. Fedorov, E.V. Fedorov, S.C. Almo, J.R. Mathiasen, D. Bozyczko-Coyne, M.S. Saporito, R.W. Scott, J.P. Mallamo, Mixed-lineage kinase 1 and mixed-lineage kinase 3 subtype-selective dihydronaphthyl[3, 4-a]pyrrolo[3, 4-c]carbazole-5-ones: optimization, mixed-lineage kinase 1 crystallography, and oral in vivo activity in 1-methyl-4-phenyltetrahydropyridine models, J. Med. Chem. 51 (2008) 5680–5689.
[173] M. Beloueche-Babari, L.E. Jackson, N.M. Al-Saffar, P. Workman, M.O. Leach, S.M. Ronen, Magnetic resonance spectroscopy monitoring of mitogen-activated protein kinase signaling inhibition, Cancer Res. 65 (2005) 3356–3363.
[174] B. Van Den Blink, T. Ten Hove, G.R. Van Den Brink, M.P. Peppelenbosch, S.J. Van Deventer, From extracellular to intracellular targets, inhibiting MAP kinases in treatment of Crohn's disease, Ann. N. Y. Acad. Sci. 973 (2002) 349–358.
[175] V.E. Torres, P.C. Harris, Mechanisms of disease: autosomal dominant and recessive polycystic kidney diseases, Nat. Clin. Pract. Nephrol. 2 (2006) 40–55.
[176] Y. Aoki, T. Niihori, Y. Narumi, S. Kure, Y. Matsubara, The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders, Hum. Mutat. 29 (2008) 992–1006.