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► **To cite this version:**

Eun Kyung Kim, Eui-Ju Choi. Pathological roles of MAPK signaling pathways in human diseases. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, 2010, 1802 (4), pp.396. 10.1016/j.bbadis.2009.12.009 . hal-00566733

**HAL Id: hal-00566733**

**<https://hal.science/hal-00566733v1>**

Submitted on 17 Feb 2011

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Accepted Manuscript

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PII: S0925-4439(10)00015-3  
DOI: doi: [10.1016/j.bbadis.2009.12.009](https://doi.org/10.1016/j.bbadis.2009.12.009)  
Reference: BBADIS 63055

To appear in: *BBA - Molecular Basis of Disease*

Received date: 10 September 2009  
Revised date: 26 November 2009  
Accepted date: 1 December 2009



Please cite this article as: Eun Kyung Kim, Eui-Ju Choi, Pathological roles of MAPK signaling pathways in human diseases, *BBA - Molecular Basis of Disease* (2010), doi: [10.1016/j.bbadis.2009.12.009](https://doi.org/10.1016/j.bbadis.2009.12.009)

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Pathological roles of MAPK signaling pathways in human diseases

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**ABSTRACT**

The mammalian family of mitogen-activated protein kinases (MAPKs) includes extracellular signal-regulated kinase (ERK), p38, and c-Jun NH<sub>2</sub>-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.

keywords: MAPK, JNK, p38, neurodegenerative diseases, cancer

### Abbreviations

MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH<sub>2</sub>-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; A $\beta$ , amyloid- $\beta$ ; 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.

## 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<sub>2</sub>-terminal kinase (JNK; also known as stress-activated protein kinase or SAPK). Each of these enzymes exists in several isoforms: ERK1 to ERK8; p38- $\alpha$ , - $\beta$ , - $\gamma$ , and - $\delta$ ; 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.  $\beta$ -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)- $\alpha$  and interleukin (IL)-1 $\beta$  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- $\beta$ -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].

Among 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  $\text{Ca}^{2+}$  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.

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## MAPK signaling in neurodegenerative diseases

### 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- $\beta$  ( $A\beta$ ) 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  $\alpha$ -,  $\beta$ - (also termed BACE1), and  $\gamma$ -secretases to produce non-amyloidogenic or amyloidogenic  $A\beta$  proteins [21-23] (Fig. 2A). Amyloidogenic  $A\beta$  is produced by  $\beta$ -secretase-mediated cleavage of APP at amino acid 83, whereas non-amyloidogenic  $A\beta$ , which is not toxic to neurons, is generated by  $\alpha$ -secretase-mediated APP cleavage at amino acid 99 [24, 25].  $A\beta_{42}$ , a major component of amyloid plaques in the AD brain, is an  $A\beta$  peptide with 42 amino acids that is produced by the amyloidogenic pathway. Although most  $A\beta$  proteins including  $A\beta_{42}$  and  $A\beta_{40}$  are secreted extracellularly, intracellular  $A\beta_{42}$  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  $\beta$ - and  $\gamma$ -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- $\alpha$  and IL-1 $\beta$ , all of which stimulate MAPK signaling pathways (Fig. 2C). Under conditions of oxidative stress, JNK and p38 are activated and induce expression of the  $\beta$ -secretase gene, whereas ERK1/2 negatively regulates  $\beta$ -secretase expression [44] (Fig. 2D).  $\gamma$ -Secretase is specifically activated by interferon- $\gamma$ , IL-1 $\beta$ , or TNF- $\alpha$ , and such cytokine-induced  $\gamma$ -secretase activity was found to be blocked by a JNK inhibitor and to be enhanced by expression of a constitutively active form of MEKK1, implicating the JNK signaling pathway in the regulation of  $\gamma$ -secretase activity [45]. Transforming growth factor- $\beta$ 2 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,  $\beta$ - and  $\gamma$ -secretase activity, and phosphorylation of APP and tau.

### **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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -,  $\beta$ -, and  $\gamma$ -synuclein, have been identified in humans.  $\alpha$ -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  $\alpha$ -synuclein manifest only mild abnormalities in neurotransmission [51]. However, pathological forms of  $\alpha$ -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  $\alpha$ -synuclein gene, are prone to form aggregates that trigger neuronal apoptosis [52-54].

LBs contain  $\alpha$ -synuclein that has been modified by phosphorylation [55, 56], ubiquitination [57], nitration [58], or truncation [59]. The high prevalence of such modified forms of  $\alpha$ -synuclein in the brain of PD patients suggests that they might contribute to neuronal toxicity [60]. Increased levels of  $\alpha$ -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].  $\alpha$ -Synuclein activates p38, ERK, and JNK pathways in human microglial cells, resulting in the production of IL-1 $\beta$  and TNF- $\alpha$  and consequent promotion of inflammation [67].  $\alpha$ -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 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  $\alpha$ -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, p38 phosphorylates the tumor suppressor p53, which then induces expression of the pro-apoptotic protein Bax, which in turn induces 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 activation of the JNK pathway [87-89]. Mice deficient in JNK3 are more resistant to MPTP than are 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 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  $\alpha$ -synuclein, with expression of DJ-1 mutants having been found to promote  $\alpha$ -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 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- $\gamma$ , 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  $\alpha$ -synuclein aggregates or functional deficiencies in parkin or DJ-1 in the pathogenesis of PD.

### **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 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-2L.

### **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 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].

## 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,  $\beta$ - and  $\gamma$ -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 CN1-1493, 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 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 & Technology, South Korea.

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ACCEPTED MANUSCRIPT

**Figure legend**

**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  $\beta$ -arrestin 2 for the ERK and JNK pathways.

**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  $\beta$ - and  $\gamma$ -secretase to produce the amyloidogenic A $\beta$  proteins A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> 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 A $\beta$  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- $\alpha$  and IL-1 $\beta$ , 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  $\beta$ -secretase gene. In contrast, ERK1/2 negatively regulates  $\beta$ -secretase expression.  $\beta$ -Secretase activity promotes the production of A $\beta$ . **E.** PD has been associated with functional defects in several genes. The products of these PD-linked genes include  $\alpha$ -synuclein, LRRK2, parkin, PINK1, and DJ-1. RING, a domain with E3 ubiquitin ligase activity; MLS, mitochondrial localization signal; KD, kinase domain. **F.**  $\alpha$ -Synuclein aggregates activate MAPK signaling, which mediates the induction of the pro-inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  in microglia.  $\alpha$ -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.**  $\alpha$ -Synuclein aggregates trigger ROS production by mitochondria as well as the release of cytochrome c (CytC) from these organelles into the cytosol, resulting in 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 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 activation of the ASK1-mediated cell death pathway in motor neurons.

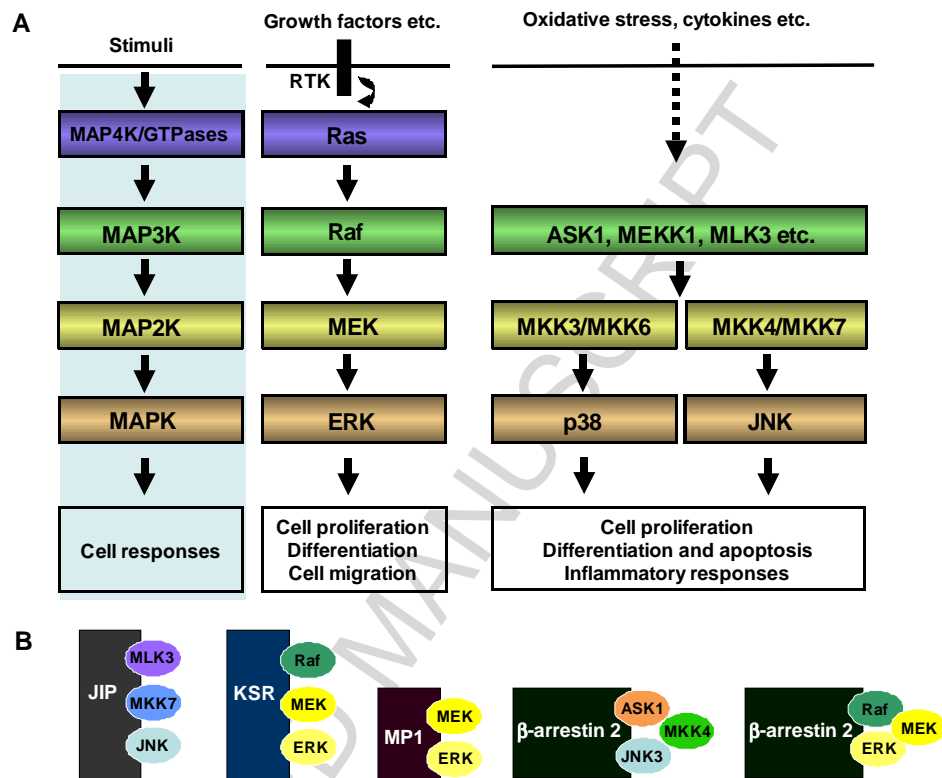


Figure 1

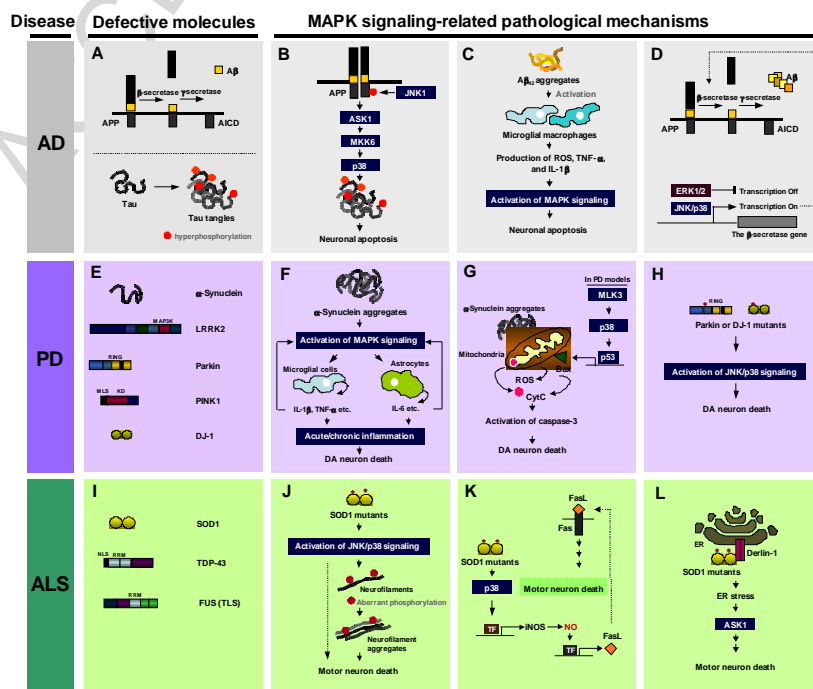


Figure 2

A $\beta$  : A $\beta$  (10-1)