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P38 MAP KINASE A NOVEL THERAPEUTIC TARGET IN NEURODEGENERATIVE DISEASES

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ABSTRACT

Inflammation in the central nervous system (CNS) is a common feature of age-related neurodegenerative diseases. Proinflammatory cytokines, such as IL-1β and TNFα, are produced primarily by cells of the innate immune system, namely microglia in the CNS, and are believed to contribute to the neuronal damage seen in the disease. The p38 mitogen-activated protein kinase (MAPK) is one of the kinase pathways that regulate the production of IL-1β and TNFα. Importantly, small molecule inhibitors of the p38 MAPK family have been developed and show efficacy in blocking the production of IL-1β and TNFα. The p38 family consists of at least four isoforms (p38α, β, γ, δ) encoded by separate genes. Recent studies have begun to demonstrate unique functions of the different isoforms, with p38α being implicated as the key isoform involved in CNS inflammation. Interestingly, there is also emerging evidence that two downstream substrates of p38 may have opposing roles, with MK2 being pro-inflammatory and MSK1/2 being anti-inflammatory. This review discusses the properties, function and regulation of the p38 MAPK family as it relates to cytokine production in the CNS.

KEYWORDS: Protein kinase; Neuroinflammation; Neurodegeneration; Microglia; Signal Transduction.

INTRODUCTION

The inflammatory response is almost always a secondary response caused by an initial event after another, like the response to trauma or infections. However, this means it is a central mech- anism in the neurodegenerative processes. It is this secondary response that will ensue and probably cause a greater loss of neurons over time as compared to the initial injury.[1] Inflammation plays a key role as a driving force that can modulate the development of

various neuropathologies. Currently the term "neuroinflammation" is used to describe the inflammatory response originated in the CNS after suffering an injury, where there is an accumulation of glial cells. Particularly astrocytes and microglia responses converge immediately after the injury occurs. In this process, cellular and molecular immune components such as cytokines, complement and pattern-recognition are contributing players, and they can lead to the activation of the glial cells, i.e., microglia and astrocytes. Innate immunity is the first line of defense of the organ- ism against different pathogens. Among the components of the response we can mention pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs), nucleotide-binding, Scavenger receptors (SRs), among others. These receptors recognize not only exogenous pathogen-associated molecular pattern (PAMP) but also endogenous modified molecules called damage- associated molecular pattern (DAMP). Throughout the body, the innate immune system launches inflammatory and regulatory responses via PRRs, phagocytes (macrophages), complement sys- tem, cytokines, and chemokines in order to counteract infection, injury, and maintain tissue homeostasis .Agents involved ininnate immunity, are directly related to agents involved in the development of neuroinflammation. Cells of the CNS such as neurons, astrocytes, and microglia along with pattern recognition receptors, cytokines, chemokines, complement, peripheral immune cells, and signal pathways constitute the basis for neuroinflammation [2]. An acute inflammatory response in the CNS is caused by the immediate and early activation of the glial cell in response to noxious stimuli, which is basically a defensive response that leads to repair of the damaged area. But, if the "stimulus" remains persistent in time, an inflammatory condition develops, causing a phenomenon of cumulative damage over time due to the chronic inflammatory reaction.[3]

It has been possible to associate a number of neurodegenerative disorders of the CNS to neuroinflammatory events, for example, based on the appearance of high levels of several pro-inflammatory cytokines: AD, Parkinson's dis- ease[4] Huntington's disease [5] multiple sclerosis (MS), amyotrophic lateral sclerosis[6] among others. In all these diseases neuropathological and neuroradiological studies have been shown.

The neuroinflammatory process. By sensing signals of damage or injury, astrocytes and microglia suffer a gradual activation process, leading to morphological changes and secretion of pro-inflammatory elements (i.e., cytokines, cytotoxic elements, ROS). Thus, the constant exposure of astrocytes and microglia to factor causing injuries and secretion of these

elements induce mutual activation of microglial cells and astrocytes, along with neuroinflammatory process that eventually trigger neuronal death.

Performed providing evidence that neuroinflammatory responses could start prior to a loss of neuronal cells. In this regard, increasing evidence has been obtained on the role of certain cytokines in the direct activation of the cellular cascade leading to neurodegeneration and AD. It would be interesting to identify as correlate the neuroinflammation levels that leading to release of these cytokines, which have neurotoxic effects and are involved in the progression of this disorder pathophysiological process.[7]

p38 MAP Kinase

p38α (p38) was first isolated as a 38 kDa protein and is known to be rapidly tyrosine phosphorylated in response to LPS stimulation.[8] p38 cDNA was also cloned as a molecule that binds puridinylimidazole derivatives which are known to inhibit biosynthesis of inflammatory cytokines such as interleukin-1 (IL-1) and tumor-necrosis factor (TNF) in LPS stimulated monocytes.[9] To date, four splice variants of the p38 family have been identified: p38α, p38β[10,11], p38γ[10,11] and p38δ (SAPK4).[12,13] Of these, p38α and p38β are ubiquitously expressed while p38γ and p38δ are differentially expressed depending on tissue type. All p38 kinases can be categorized by a Thr-Gly-Tyr (TGY) dual phosphorylation motif.[15] Sequence comparisons have revealed that each p38 isoform shares~60% identity within the p38 group but only 40- 45% to the other three MAP kinase family members.[16]

Localization of p38 MAPK in Brain

Despite an abundance of data concerning p38 activation and function in peripheral tissues, the role of p38 in the brain is poorly understood. This is surprising while considering the fact that p38 is more highly expressed in brain than in peripheral tissues.[9,15] Only the p38α and p38β isoforms are expressed in the brain, with high levels of protein in most major brain regions, including cerebral cortex, hippocampus, cerebellum, and several brainstem nuclei.[8] Detected mainly in neurons, p38α is found in the nucleus, dendrites, and in cytoplasmic regions of the cell body. Both neurons and glia express p38β, with a pronounced nuclear location. Theα and β isoforms of p38 are especially enriched in hippocampus, the brain region predominantly involved in learning and memory. Further, they are heavily expressed in pyramidal neurons of CA1 and CA3 regions of hippocampus as well as in granule cells of the dentate gyrus.[16] Unlike p38α, p38β is detected in glial cells of the CA1 region also. In addition to prominent mRNA and protein levels, p38 also exhibits a high basal activity in

brain[17], which suggest that the p38 pathway may play a role in normal neuronal function in addition to its role as an SAPK. Unlike JNK, whose function(s) are preferentially related to the control of apoptosis, p38 in the brain is involved not only in apoptosis, but also in aspects of neuronal differentiation, synaptic function and neuronal plasticity. Additionally, the p38 pathway is active during the induction of long-term depression (LTD), a form of plasticity that is the functional inverse of LTP and is involved in associative learning.

MAP Kinase Pathway at a glance

p38 MAPK (mitogen-activated protein kinase) signaling cascade provides a mechanism for cells to respond to a catalogue of external mitogens (signals) and respond accordingly by mediating a wide range of cellular effects. In fact, the diversity and specificity in cellular responses as depicted by the cascade is facilitated via a simple linear architecture, which comprises of sequentially operating core of three evolutionarily conserved protein kinases namely; MAPK, MAPK kinase (MAPKK), and MAPKK kinase (MAPKKK). MAPKKKs are serine/threonine kinases, which are activated via phosphorylation and/or because of their interaction with a small GTP-binding protein of the Ras/Rho family in response to extracellular stimulus. MAPKKK activation results in phosphorylation and activation of MAPKKs, which consequently stimulate MAPK activity through dual phosphorylation of threonine and tyrosine residues positioned in the activation loop of kinase subdomain VIII.[33] The activated MAPKs now phosphorylates target substrates specifically on serine or threonine residues followed by a proline. MAPKKs such as MEK3 and MEK6 are activated by a wide range of MAPKKKs (MEKK1 to 3, MLK2/3, ASK1, Tpl2, TAK1, and TAO1/2), which themselves become activated in response to oxidative stress, UV irradiation, hypoxia, ischemia, and cytokines, including interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α).[34] At present, five different MAP kinases (MAPks) have been characterized and investigated namely; extracellular signal-regulated kinases (ERKs) 1 and 2 (ERK1/2), c-Jun amino-terminal kinases or stress-activated protein kinases (JNKs/SAPKs) 1, 2, and 3, p38 isoforms α, β, γ, and δ, ERKs 3 and 4, and ERK5. The kinase p38α (p38) was initially isolated as a 38-kDa protein which was observed to be rapidly phosphorylated at tyrosine motifs in response to LPS stimulation. Later, p38 was cloned and studied as a molecule capable of binding puridinyl imidazole derivatives; these derivatives inhibit the biosynthesis of inflammatory mediators like interleukin-1 (IL-1) and tumor-necrosis factor (TNF) in LPS activated monocytes. p38 (also known as CSBP, mHOG1, RK, and SAPK2) kinases are more responsive towards stress stimuli such as osmotic shock, ionizing radiation, and cytokine

stimulation and four different variants of p38 arising out of alternative splicing are known viz. p38α, p38β, p38γ (ERK6, SAPK3), and p38δ (SAPK4). Among these, p38 and p38β are ubiquitously expressed in tissues, whereas, p38γ and p38δ show variegated expression in a tissue specific manner.[35] Each of the p38 variants comprises of a Thr- Gly-Tyr (TGY) dual phosphorylation motif and sequence comparison performed earlier suggests that each p38 isoform shares approximately 60% density with other members of the p38 group but only 40-45% with other MAP kinase family members. The activity of p38 is controlled and coordinated in vitro by three different kinases: MKK3, MKK4, and MKK6. In vivo, MKK3 and MKK6 are necessary for tumor necrosis factor- stimulated p38 MAPK activation whereas, ultraviolet radiation-mediated p38 MAPK activation requires MKK3, MKK4, and MKK6.[25] p38 isoforms can also be stimulated by GPCRs and by Rho family GTPases; Rac and Cdc42. It is interesting to mention here that MAPKs catalyse the phosphorylation and activation of several protein kinases, termed MAPK-activated protein kinases (MKs), which represent an additional enzymatic step in the MAPK catalytic signaling cascade. MEK3 and MEK6 do not participate in the activation of ERK1/2 or JNK and display a high degree of specificity for p38. In addition, MEK4 (MKK4/Sek1) JNK kinase show limited MAPKK activity toward p38. MEK6 is capable of activating all the p38 isoforms, whereas, MEK3 is discerning and preferentially phosphorylates the p38α and p38β isoforms. p38 isoforms are activated as a result of MEK3/6-catalyzed phosphorylation of Thr-Gly-Tyr (TGY) motif in the p38 activation loop. The differential specificity in p38 activation results from the formation of functional complexes between MEK3/6 and different p38 isoforms and the selective recognition of the activation loop of p38 isoforms by MEK3/6. The length of the phosphorylated TGY motif and the activation loop is different in other MAPKs namely ERK2 and JNK, which likely contributes to the p38 substrate specificity. P38 substrates include cPLA2, MNK1/2, MK2/3, HuR, Bax, and Tau in the cytoplasm and ATF1/2/6, MEF2, Elk-1, GADD153, Ets1, p53, and MSK1/2 in the nucleus (36). Emerging proofs advocate a role for the p38 MAPK and MKP-1 in the maintenance and demise of dopaminergic neurons. Mitogen-activated protein kinase phosphatase-1 (MKP-1) is a negative regulator of p38 activity and other MAPKs such as ERK, and c-Jun NH (2) -terminal kinase (JNK). MKP-1 was found to be expressed in DA neurons cultured from E14 rat ventral mesencephalon (VM) and it was reported that DA neurons when transfected to overexpress MKP-1, triggered a substantial increase in neurite length and branching with maximum upsurge observed in primary branches.[37] In addition, DA neurons displaying over-expressed MKP-1 patterns are subjected to neuroprotection against the effects of PD

inducing neurotoxin 6-OHDA. MKP-1 can also promote the growth and elaboration of dopaminergic neuronal processes suggesting that MKP-1 is actively involved in DA neuronal maintenance and therefore deviant MKP-1 expression is a hallmark of damaged DA neurons in PD.[38] Therefore, formulating strategies aimed at augmenting MKP-1 expression to appropriate p38 activity may be advantageous in shielding dopaminergic neurons from PD induced damage.[39]

The role of p38 MAPK and its substrate MAPK activated protein MAPKAP Kinase (MK) MK-2 in neuroinflammation

Several p38 MAPK targets are kinases and transcription factors, known to play a role in inflammation via the production and activation of inflammatory mediators. It is known that p38 MAPK becomes activated by many cellular stresses besides inflammatory cytokines.[19,20] The identification of p38 MAPK (an isoform of p38 MAPK) activation residues[21] and the discovery of MK2 as being a direct substrate of p38 MAPK, provided the first indications of the possible molecular mechanisms that could be involved in the activation of p38 MAPK cascades.[22,23] MAPKAP Kinases (MKs), MAPKAPK-2 (MK-2) and MAPKAPK-3 (MK-3) are serine/threonine kinases are part of the subfamily that bind to and are specifically activated by the p38 MAPK isoforms.[24,25] MK-2 is recognized as the most important kinase to be activated by p38 MAPK since it has a vital role in mediating both cellular stress and inflammatory responses. The p38 MAPK/MK-2 complex has been documented to contribute to inflammation in vivo, since MK-2 knockout mice are resistant to endotoxic shock as a result of lipopolysaccharide (LPS)-stimulation.[26] MK-2 is involved in regulating the production of TNF-, IL-6, IL-8, and several other cytokines that play a role in inflammation.[27,28] MK-2 expression and activation is increased in microglia that have been stimulated with LPS- and interferon-, and microglial cells cultured from MK-2 knockout mice showed a reduction in the levels of inflammatory cytokines.[29] This signaling is of particular interest as the p38 MAPK/MK-2 pathway and the consequent production of inflammatory cytokines have a significant role in neurodegenerative disease processes where oxidative stress and persistent neuroinflammation are the primary causes of disease. MAPKAP kinase-2, one of p38 MAPK's more prevalent substrates has also been implicated in Parkison's disease (PD), where it has been shown that MK2-deficient mice show decreased levels of neuroinflammation and loss of dopaminergic neurons within the substantia nigra after treatment with the Parkinson's inducing neurotoxin 1-methy-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) compared to MK-2 wild-type mice.[30]

MAPK p38 and its substrates have been shown to modulate neuronal plasticity and have been implicated in several neurodegenerative diseases. The release of pro- inflammatory cytokines as a result of activation of the p38 MAPK cascade, has been reported to be involved in AD, PD, MS, cerebral ischemia, depression and neuropathic pain.[31] The activation of p38 MAPK signaling mediates changes in morphology and density of dendritic spines seen during the development of neurodegenerative disease and is associated with memory impairment after epileptic seizures.[31] The understanding of the functional role of the p38 MAPK signaling cascade in affecting synaptic plasticity in the hippocampus and its potential role in neurodegenerative diseases such as AD has made significant progress. Several formulations of p38 MAPK inhibitors are being actively screened in phase II clinical trials for depression. Evaluation of MAPK p38 inhibitors as therapeutic agents in neural diseases is an active area of research and they are being rigorously explored in both preclinical experimental models in addition to clinical trials for various inflammatory diseases.[32]

Implication of P38 MAPK in various neurodegenerative diseases

Alzheimer's disease (PD)

P38 has been demonstrated in vitro to phosphorylate tau on residues known to be phosphorylated in NFTs extracted from AD brains.[25,48,50] However, many other kinases, such as glycogen synthase kinase (GSK)-3β and extracellular signal- regulated kinase (ERK)-2, have also been implicated as tau kinases, with different kinases demonstrating different preferences for certain sites (50). Many of these kinases, including p38, have been demonstrated to phosphorylate tau when co-transfected with tau into cells, with GSK-3β demonstrating the best activity.[51,52] Although encouraging, the extrapolation of these data to AD is limited by caveats around overexpression and the use of non-neuronal cells. Therefore, current knowledge does not indicate the best target for intervention in tau phosphorylation in vivo, and further elucidation in this area is required. Additionally, it is not known if inhibition of any single kinase will have an impact on NFT formation. Although p38 has been implicated in tau phosphorylation in vitro and is associated in activated form with NFTs in AD in situ, there is currently no evidence that p38 phosphorylates tau in vivo. The activation of p38 has been demonstrated concurrently in conjunction with tau phosphorylation in the brains of rats implanted with IL-1- impregnated pellets; however, these results remain correlative.[13,53] Recently, p38 activation has been demonstrated in a murine amyloidogenic model of AD in which mutated APP is overexpressed, and activation correlated with plaque

burden and tau phosphorylation in the brains of these mice.[8] Assessing a p38 inhibitor in such a model may elucidate the role of p38 in tau phosphorylation and plaque formation in vivo. However, it is important to keep in mind that although these mice appear to show some degree of tau hyper phosphorylation, they do not develop NFTs. Thus, the implications of decreasing tau phosphorylation on NFT formation for any therapeutic approach cannot be assessed in this model. Other transgenic mice, which overexpress tau alone or tau and APP, have been reported to form tangle-like structures and may therefore be useful tools for assessing potential therapeutics on NFT formation in vivo.[54-56] However, to date, the activation of kinases in these models has not yet been characterized.

p38 MAPK activation In Amyloid-beta The in vitro effect of Aß on p38 in neurons is also controversial with a debate on whether Aß activates p38 in neurons. One research group has reported that Aß activates p38 in N2 neuroblastoma cells[7], while two other groups have not reported any such effect.[57,58] The recent finding that p38 is activated in double transgenic mice expressing AßPP (K670N/ M671L) and PS1 (P264L)[59], as determined by immunobloting, has shown that Aß activates p38 in vivo. However, due to the lack of concurrent immunocytochemistry data, it is not clear whether this is microglial or neuronal in origin. Neuronal accumulation of Aβ has been implicated as a cause of the neuronal loss that occurs in AD while previous studies have shown that Aβ is cytotoxic to neurons, at least in cell culture. The mechanisms and signaling pathways involved are just beginning to be unraveled. It has been reported that Aβ induces the activation of p38 in a concentration-dependent manner in both M17 human neuroblastoma cells and primary cortical neurons. Since Aβ is present at up to micromolar concentration with the development of amyloidal deposits, these findings suggest that the chronic exposure to high Aβ levels may also be responsible for the abnormal activation of p38 in AD brain.[60,61] Some studies have demonstrated that inhibition of the p38 pathway either by overexpressing the dominant negative p38 or by specific pharmacological inhibitor such as SB203580 results in decreased Aβ-mediated cytotoxicity indicating an important role for p38 in the toxication of Aβ. However, since overexpression of dominant negative p38 or application of SB203580 does not completely block Aβ-induced neuronal death, it is likely that p38 regulates neuronal death in concert with other signaling transduction pathways. In this regard, previous studies demonstrate that a related pathway, namely the JNK pathway, is also activated in cultured neuronal cells after exposure to Aβ and that inhibition of JNK also partially attenuates Aβ-induced cytotoxicity.[57,58,62,63] Therefore, it is conceivable that both the JNK and p38

pathways work synergistically in mediating Aβ- induced neuronal death. In support of such a concept, another reports demonstrated a nearly complete overlap between phospho-JNK and phospho-p38 in severe AD cases implying that JNK and p38 are both activated by the same signal and, as such, work synergistically in vivo.[60,61] It will now be of great interest to establish the mechanism by which Aβ induces the activation of p38. In this regard, since Aβ appears to bind to the surface of neurons through multiple receptors, and one or more of them may be involved in Aβ-induced p38 activation, it is anticipated that the different receptors involved may lead to distinct responses. For example, the receptor for advanced glycation end products (RAGE), which interacts with Aβ may be a good candidate that is specifically involved in mediating Aβ-induced oxidative stress through the p38 pathway.[64] Also it is notable that Aβ binding of AβPP Induces AβPP dimerization which, in turn, activates ASK1/MKK6/p38 cascade. It will also be important to characterize the mechanisms by which p38 activation leads to cell death. One possible target is TNF-α, because the expression of TNF-α is regulated by p38.[65] More relevantly, the levels of both TNF-α are elevated in AD.[66,67] Therefore, the characterization of specific receptors as well as the downstream targets involved in Aβ-mediated events will not only help to better understand the nature of Aβ action but also identify specific targets for interrupting the pathogenesis process.

Parkinson ‘disease (PD)

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.[61,62]

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[63], although its cellular functions remain unclear. Mice lacking α-synuclein manifest only mild abnormalities in neurotransmission.[64] 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.[65,66,67]

LBs contain α-synuclein that has been modified by phosphorylation. Ubiquitination, nitration, or truncation. The high prevalence of such modified forms of α-synuclein in the brain of PD patients suggests that they might contribute to neuronal toxicity. Increased levels of α-synuclein are thought to be associated with neuronal apoptosis induced by oxidative stress, neuroinflammation, or dysfunction of MAPK signaling pathways.

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. 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. α-Synuclein also induces the expression of IL-6 and intercellular adhesion molecule-1 (ICAM-1) in human astrocytes and thereby promotes chronic inflammation. The up-regulation of these latter two proteins is also associated with the activation of MAPK signaling pathways. 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.[67]

Amyotrophic lateral sclerosis (ALS)

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. Aberrant expression and activation of p38 MAPK in motor neurons and microglia are thought to be important for ALS progression [68]. Persistent activation of p38 correlates with degeneration of motor neurons in transgenic mice expressing the G93A mutant of SOD1. Moreover, a p38 MAPK inhibitor, SB203580, prevents the apoptosis of motor neurons induced by mutant SOD1. 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 [69]. Signaling by p38 MAPK mediates Fas-dependent apoptosis through up-regulation of NO production in motor neurons. Exogenous NO also induces expression of Fas ligand and thereby stimulates Fas signaling, which triggers activation of the p38 pathway and NO synthesis. Motor neurons of transgenic mice expressing mutant SOD1 (G93A or G85R) are more sensitive to NO than are those of control mice.

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

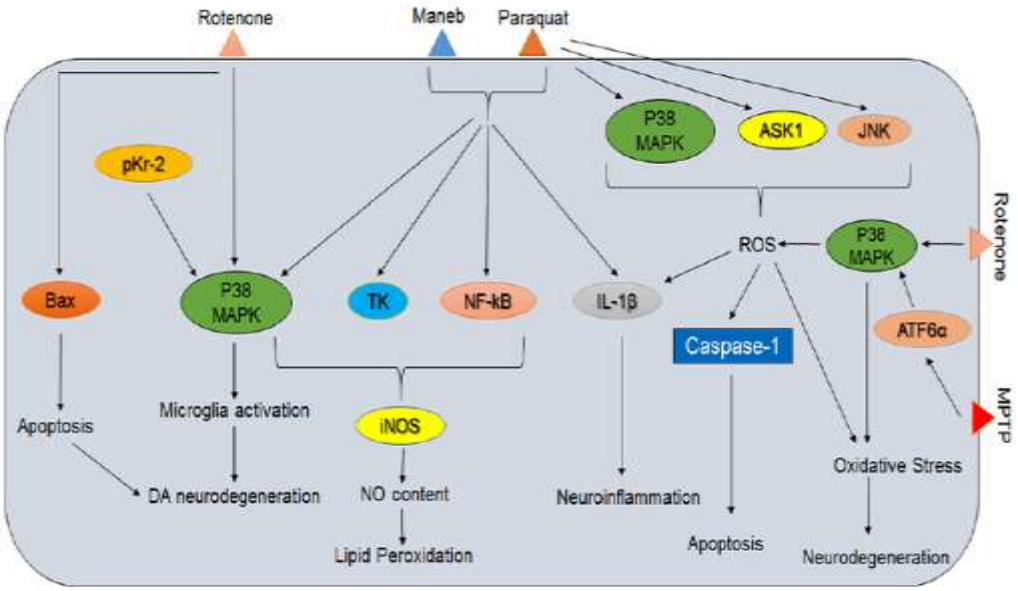

Fig-1

Concluding remarks

MAPK signaling pathways have been implicated in the pathogenesis of a variety of 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 hyper phosphorylation of tau, have been widely investigated as potential therapeutic drugs for AD. 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. 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.[70] 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.[71] 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. 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.[72]

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