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The JNK signalling transduction pathway in the brain

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1. ABSTRACT

Among the numerous intracellular signalling pathways that control brain development and pathogenesis c-Jun N-terminal kinases have a leading role in the Central Nervous System. JNKs regulate a wide range of processes in brain development, plasticity, repair/regeneration, neuronal death and neuroinflammation. Indeed, accumulating evidence underline the potential of JNK targeted molecules towards the treatment of neurodegenerative disorders. The focus of the presenting review is to provide an overview of the reported data linking JNKs to brain function and dysfunction.

2. INTRODUCTION

Neurons respond to extracellular changes with the activation of signalling pathways that mediate signal transduction from the cell surface to the nucleus. These pathways serve to transmit, amplify and integrate signals resulting in a physiological response. In the Central Nervous System such signals mediate brain development, repair, neuronal death and neuroinflammation. The c-Jun NH_2-terminal kinase (JNK) pathway is one such family of evolutionarily conserved serine/threonine kinases signalling proteins with a determinant role in development and disease.

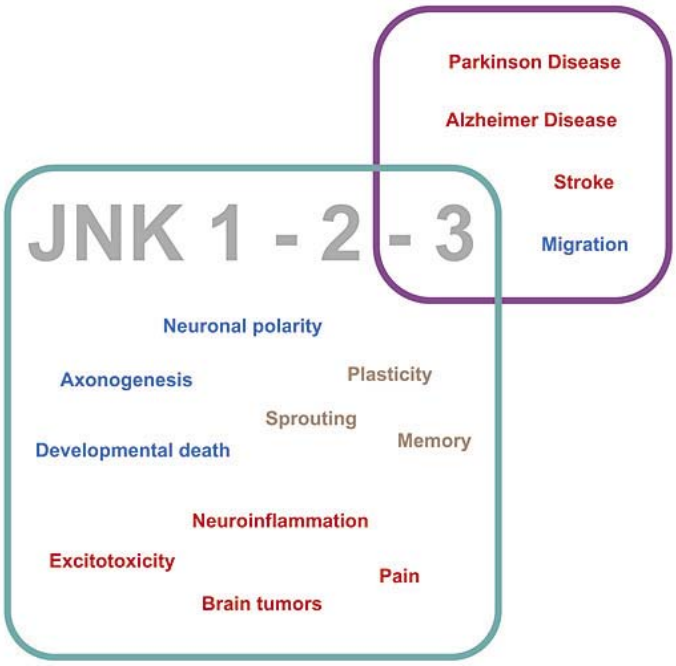

Figure 1. Simplified diagram of the role of JNKs in brain.JNK1 and 2 isoforms are mainly involved in brain development (see blue words in the big square box), while JNK3 has a much smaller role. JNK1 and 2 participate in physiological regulation of adult brain (see words in gray in the bigger box) but also in pathological conditions (red words in boxes). JNK3 is less involved in brain development (a part migration-blue) but mainly contributes to brain pathologies, in particular in Alzheimer disease, Parkinson disease and Stroke (red words in the little square box). Blue words summarize developmental, gray physiological and red pathological roles of JNK in the brain.

JNKs are involved in numerous cellular processes that include proliferation, differentiation and apoptosis. The determinant role of JNKs in apoptosis has been extensively studied (For an extensive review see Davis (1)). Diverse signals such as DNA damage, oxidative stress and aging all lead to upregulation of JNKs, which on their turn regulate key pro- and anti-apoptotic proteins. Intriguingly JNK basal activity is higher in the brain than in other tissues (2), a finding that underlines the important role of JNK in normal physiological functions of the nervous system (Figure 1).

The focus of this review is to describe the current knowledge of JNK in brain function and dysfunction.

2.1. JNK signalling pathway

The JNK signalling cascade has been extensively studied and is well characterized (1). Briefly, JNKs reside in the cytosol where they are activated by simultaneous phosphorylation of threonine and tyrosine residues present in the conserved Thr-Pro-Tyr motif within their activation loop. This dual phosphorylation is mediated by MKK4 and MKK7, members of the family of dual-specificity kinases referred to as MAPK kinases (MAP2Ks) (3). Concomitantly, JNK activation is regulated by dephosphorylation of two phosphatases MKP-1, M3/6 and MKP7 (4-6). Another important and most probably key mechanism to control efficiency and specificity of JNKs is mediated by scaffold proteins that bind and sequester JNK in different cellular compartments, and subsequently minimize and/or inhibit other MAPK cross-talks (7, 8).

On their turn, activated JNKs phosphorylate over 60 substrates, amongst them a variety of nuclear factors such as c-Jun, ATF2 and Elk but also cytoplasmic substrates such as cytoskeleton proteins, or mitochondrial proteins like Bcl-2 and Bcl-xl, and also the glucocorticoid receptor, the amyloid precursor protein (9) membrane protein (10, 11).

Unfortunately very little has been done on the role of JNK in physiological conditions while something more is known in the pathology, particularly during inflammation. In this review we will focus our attention on the role of JNK in neurons, but it should be considered that also astroglia and microglia express JNKs.

3. ROLE OF THE JNK PATHWAY IN THE DEVELOPING BRAIN

The overall contribution of JNK signalling in brain development results from the wide-range of basal functions such as the regulation of region-specific neuronal death (2), migration, neuronal polarity (12, 13) as well as axonogenesis (14).

Back in 1999, Kuan et al. (2) described the critical role of JNK1 and JNK2 kinases during brain development and in the regulation of regional specific apoptosis. During development the three isoforms show a distinct spatial as well as temporal distribution. Whereas

the JNK1 and JNK2 isoforms are detected as early as embryonic day E7, the JNK3 isoform is detected after embryonic day E11. Interestingly, mice deficient in any of the three genes are viable without apparent morphological abnormalities. Such findings suggest that the JNK isoforms can compensate for each other. Nevertheless healthy Jnk1/Jnk3 and Jnk2/Jnk3 compound mutants survive perfectly. On the contrary, Jnk1/Jnk2 mutants are embryonic lethal and show severe dysregulation of early brain apoptosis. A very recent study by Xu *et al.* (15) reported the creation of mice with triple deficiency of neuronal JNKs. Triple JNK knockout neurons exhibit hypertrophy, a reduction in the number of dendrites, and increased life-span *in vitro*. The above findings highlight the importance of JNK signalling as a whole for normal neuronal function but also imply that JNK3, a key kinase in brain disease, is dispensable for brain development in rodents. Still some controversy exists concerning the contribution of JNK3 in brain development since a study by Gelderblom *et al.* (16) demonstrated that the differentiation of primary hippocampal neurons from neonatal JNK3 knockout mice display an increase in activated caspase 3. In line with Gelderblom *et al.* (16), Shoichet *et al.* (17) showed that an autosomal-recessive disruption of the JNK3 gene in humans results in the expression of a truncated JNK3 protein, which on its turn causes epileptic encephalopathy and severe mental retardation (17). In neuronal cells this truncated form of JNK3 disrupts normal JNK3 signal transduction and tends to form aggregates in the cytoplasm, as opposed to the wildtype JNK3 which is uniformly expressed both in the cytoplasm and the nucleus. Nevertheless these are the only reports that support a role for JNK3 in normal brain development.

JNKs are also involved in neuronal migration, a fundamental step in brain development and function. JNK activity is higher in cortical layers or areas of migrating neurons (18). Generally it is thought that JNKs regulate neuronal migration via phosphorylation of cytoskeletal proteins such as doublecortin (DCX) and consequently by modulation of microtubule dynamics (18).

In a similar manner, the involvement of JNKs in axonogenesis, dendritic formation and elongation, branching and sprouting-all processes that contribute to the normal functioning of the CNS- has been extensively covered (Figure 1). The role of JNKs in the regulation of the neuronal cytoskeleton was initially indicated by their predominant distribution within cytoskeleton-associated structures such as synapses, growth cones and cell membranes in primary hippocampal neurons. Functional deletion of JNK1 results in atrophy of cerebral fiber tracts and dendritic spines in young mice (19). Alongside, Chang *et al.* clearly demonstrated that cytoplasmic JNK1 phosphorylates neurofilaments and microtubule-associated protein (MAP), thus being essential for microtubule stability (19, 20). Additionally, cytoplasmic JNK substrates such as DCX, and SCG10 are involved in promoting neurite extension and stability (19, 21).

Similar to JNKs, the JIP scaffold proteins accumulate in axonal and dendritic growth cones and are present at synapses. JIP1 and JIP3 contribute in the organization of JNK-mediated microtubule dynamics underlying neurite outgrowth and cell polarity (12, 13). Studies of JIP homologues in lower eukaryotes and recent gene targeting studies in mice support the notion that JIPs are the main scaffold proteins for JNK activation during development (22). Mutations of the genes encoding JIP1 (*Aplip1*) or JIP3 (*Syd*) in *Drosophila* reduce axonal anterograde and retrograde vesicle transport (23). Furthermore, *Aplip1* mutants display reduced retrograde transport of mitochondria consistent with defective dynein action (23). Similar results have been reported with JIP3 (*UNC-16*) mutants in *C. elegans*. In mice, targeting of the *JIP3* gene leads to loss of the telencephalic commissure and a disorganized telencephalon, suggestive of a defect in axon guidance and reduced vesicle transport. Contrary to the results obtained in Drosophila studies, JIP1-deficient mice do not display abnormalities in brain anatomy and develop normally, suggesting that either mammalian JIP1 is not essential for axonal transport of vesicles and axon guidance (7) or that the other JIP proteins may compensate for the loss of JIP1. Functional redundancy between the JIP family members is supported by the finding that transgenic expression of JIP1 in the JIP3-null mice can partially rescue the axon guidance defects observed in the JIP3-null mice (22).

It should be noted that although JNKs have an established role in the neuronal processes outlined in this section, equally important roles have been attributed to other kinases, such as the MAPK extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphoinositide-3-kinase (PI3K) (24, 25). New evidence suggests cross talks, e.g. between Wnt signalling and JNKs, whereby JNKs stabilize microtubules (26).

4. PHYSIOLOGICAL ROLE OF THE JNK PATHWAY IN THE ADULT BRAIN

The high level of basal JNK activity in the adult nervous system suggests a role for this kinase in normal physiological functions (2); however this is partially unexplored.

Some evidence has pointed out the importance of JNK in various aspects of plasticity, learning and memory formation (Figure 1). For instance, JNK is involved in low frequency, stimulation-dependent long-term depression (LTD) in the dentate gyrus, and in memory consolidation during associative learning under stressful and baseline conditions (27).

JNK is activated in the insular cortex when exposed to a novel taste underling the contribution of JNK in brain plasticity in physiological conditions (28). Similarly, the inhibitory effect of interleukin-1β on hippocampal LTP is associated with an increase in JNK activity (29). Noteworthy, JNKs are implicated in membrane receptor mobility and in particular in AMPA-R trafficking following changes in neuronal activity (30). Last but not least a report by Bevilaqua *et al.* (31) indicated a differential role for hippocampal JNK in short- and long-term memory.

The exact molecular mechanisms by which JNKs contribute to learning processes are far from being understood. Nonetheless, potential downstream candidates regulated by JNKs may be proteins such as: synaptotagmin-4 (32) cytoskeletal proteins such as MAPs (11), the AMPA receptors (30), or transcription factors, including c-Jun, activator transcription factor (ATF-2), CREB (calcium/cAMP response element binding protein), and Elk-1 (10). Such substrates are good candidates in JNKs-mediated pathways during learning since not only they interact with JNK but they are also involved in memory processes.

Apart from these findings that underline the contribution of JNKs in plasticity and cognitive function little else is known about the role of JNK in physiological conditions in the adult brain.

5. PATHOPHYSIOLOGICAL ROLE OF THE JNK PATHWAY IN THE ADULT BRAIN

Neurodegenerative disorders ranging from acute ones, such as stroke, to chronic ones, such as Alzheimer's and Parkinson's Diseases, are all characterized by irreversible neuronal loss that is often the consequence of a number of factors, ranging from genetic to environmental ones

The importance of JNKs in these multifactorial disorders (Figure 1) lies on the fact that they are activated by a variety of stress signals and their function is well-established in apoptosis, necrosis and autophagic cell death. Deletion or inhibition of JNKs prevents the initiation of death programs in neurons; as such drugs that target the JNK pathway are particularly appealing (33).

In the following sections we will summarize the most important discoveries concerning the involvement of JNK signalling in major neurodegenerating disorders.

5.1. Excitotoxicity

We first consider excitotoxicity because this is the main mechanism responsible for neuronal death in many neurological conditions including cerebral ischemia/hypoxia, traumatic brain injury and also chronic neurodegenerative diseases.

Excitotoxicity is defined as the excessive activation of glutamate receptors, in which *N*-methyl-D-aspartate (NMDA) receptors play a key role as a result of their high Ca^{2+} permeability. Over-activation of NMDA receptors induces a downstream cascade of events leading to neuronal death.

In cortical neurons exposed to high concentrations of NMDA (100 microM), JNK pathway is tightly connected to extracellular calcium influx (34) and plays a pivotal role in inducing and executing the death pathway. The cell permeable JNK inhibitor peptide D-JNKI-1 completely inhibits cell death induced by excitotoxicity (35). Moreover application of NMDA (100microM) in organotypic hippocampal cultures leads to death of pyramidal neurons in the CA1 and CA3 regions, already detectable within two hours. In the same regions, c-jun is selectively phosphorylated and c-fos is up-regulated. Pretreatment with 2microM D-JNKI-1 prevents pyramidal neurons death and completely inhibits c-jun phosphorylation and c-fos expression (36). Moreover, mice with an inactive form of c-jun (Jun AA, in which serines 63 and 73 are mutated to alanines) also show resistance to excitotoxic neuronal death, suggesting that preventing JNK from accessing c-jun may confer neuroprotection (37).

5.2. Stroke

Stroke is a large cause of death and disability in the world. Failure to develop effective treatments is most likely because current models disregard the long therapeutical time window required in clinics.

JNKs are interesting targets in stroke therapy due to their key role in programmed cell death but most importantly because JNK activation overlaps with the required time to reassure therapeutic success. In rat hippocampal CA1 neurons, JNK activity increases at 6 hours and lasts up to 3 days after global ischemia and between 0.5 and 24 hour following transient focal ischemia (38). Repici *et al.* (39) also showed that in rat cerebral ischemia JNK activation starts at 3 h and peaks at 6 h in the ischemic core and at 1 h and at 6 h in the penumbra.

Several partners of JNKs in programmed cell death (PCD) have been identified and help to explain the powerful role of JNK in ischemia. These include the pro-death proteins such as the Bcl-2 family proteins, caspase 3 as well as the transcription factors c-jun, c-fos that on their turn upregulate the expression of pro-death proteins (35) (40, 41).

The contribution of JNKs and especially of JNK3 in stroke is well characterized. Kainate mediated neuronal death is reduced in the hippocampus of JNK3-deficient mice (42). Numerous studies followed to show that JNK3, but not JNK2 or JNK1 knockout mice, are protected from ischemia-hypoxia brain injury (2) as well as an effect of JNK inhibition on neuronal excitation (43).

The above data are supported by a number of pharmacological studies with inhibitors of the JNK signalling pathway. Inhibition of JNK via intracerebroventricular injection of the pharmacological inhibitor SP600125 after focal ischemia provides robust neuroprotection (44). Additionally, administration of D-JNKI1 provides neuroprotection and prevents from behavioural consequences in both transient and permanent middle cerebral artery occlusion in adult mice and rats respectively (35). This study is of major clinical relevance since the D-JNKI1 peptide was administered 6 hours after transient ischemia and 12 hours after permanent ischemia and it could still prevent neuronal death and confer neurobehavioral benefits up to 14 days of reperfusion (35). A number of reports followed that fully support the efficacy of the D-JNKI1 peptide in ischemic brain injury (35, 45, 46). More indirect, but nonetheless interesting data have been published on the use of Tat-GluR6-9c peptide (a glutamate receptor 6 C-terminus peptide fused the TAT

protein transduction sequence) that disrupts the assembly of the GluR6-PSD95-MLK3 module and suppresses the activation of MLK3, MKK7 and JNK (47). Intracerebroventricular injection of the Tat-GluR6-9c was successful in diminishing kainate-induced neuronal cell death in adult rats and conferred neuroprotection in a model of focal ischemic brain insult on rat middle cerebral artery occlusion. Similarly, application of the peptide rescued neurons in an *in vitro* model of oxygen-glucose deprivation (48). Overall these studies underline the pivotal role of JNK signalling pathway in stroke in inducing and executing neuronal death. (Figure 1).

5.3. Alzheimer's disease (AD)

AD is a multifactorial disease where different processes contribute and lead to synaptic and neuronal dysfunction. Accumulating data support the notion that JNK is a key player in AD pathology (Figure 1). In AD brain, increased activity of JNK is observed in neurons and dystrophic neuritis (49, 50) JNK activation is associated with tau-induced neurodegeneration (51) and Abeta pathology (52), the two hallmarks of AD pathology. JNK pathway is activated in both cortical neurons treated with Aβ25-35 and differentiated PC12 cells after exposure to aggregated Aβ41-42 (53-55). Inhibition of the JNK pathway significantly reduces the toxicity attributable to Aβ in both cases. The JNK3 isoform seems to have a central role in AD. JNK3 is the major kinase for APP phosphorylation at T668 (9) and is highly expressed and activated in postmortem brains of AD patients (50). Some more recent data demonstrated the contribution of JNK3 on tau hyperphosphorylation (56). Last but not least, neurons derived from JNK3-/- mice are resistant to Aβ-induced apoptosis when compared with neurons from normal mice.

Some of the partners of JNK in Abeta-induced neurodegeneration have been identified. JNKs are involved in Abeta-triggered downregulation of the anti-apoptotic Bcl-w (57) and activation of Toll-like receptor 4 (TLR4) signalling. Neurons from TLR4 mutant mice exhibit reduced JNK and caspase-3 activation and are protected against Abeta-induced apoptosis (58).

Studies with specific inhibitors of JNKs emphasize the role of JNK in AD. The D-JNKI1 peptide inhibitor diminishes efficiently the production of Abeta precursor protein and Abeta-fragments both in cortical neurons as well as in an *in vitro* model of AD (52, 59). Similarly, neuronal death is blocked by D-JNKI1 in a brain slice model for amyloid precursor protein-APP-induced neurodegeneration (60).

We indeed, believe that JNK has a determinant role in AD pathology. It is possible that a stressor(s), such as aging, accumulated oxidative stress, and/or inflammation, activates JNK leading to changes in APP metabolism, tau phosphorylation, synaptic/neuritic dystrophy, or glial activation. Positive feedback loops may be present in the AD brain whereby the initial stressor is further amplified via JNK activation. As such, JNK becomes the main actor and consequently an attractive therapeutic target against AD pathogenesis.

5.4. Parkinson's disease (PD)

Parkinson's disease is a motor system disorder and the second most common neurological disorder (61). In patients with PD, 80 percent or more of the dopamine-producing cells-responsible for smooth movement of muscles- are damaged, dead, or otherwise degenerated. Myriads of evidence exist to support the contribution of JNK in PD (Figure 1).

Overexpression of parkin, a protector of dopaminergic neurons and the most common gene mutated in autosomal recessive familial parkinsonism, significantly attenuates dopamine-induced activation of JNK in SHSY5Y cells (62). Conversely, JNK is highly activated in dopaminergic neurons of Drosophila *parkin* loss of function mutants (63). Parkin has also been reported to directly inhibit JNK activation via ubiquitination of JNK pathway mediators (63).

Similarly, increased kinase activity is observed in pathogenic mutants of Leucine-Rich Repeat Kinase 2 (LRRK2), another gene involved in PD pathogenesis and induces PD-associated neurotoxicity (64). Interestingly, leucine-rich repeat kinase-2 shares high sequence homology with mixed linage kinases, which act upstream of MAPKK and are involved in cellular stress responses. *In vitro*, LRRK2 variants phosphorylate mitogen-activated protein kinase kinases (MAPKK), including MKK3 -4, -6 and -7, MKK4 and MKK7 being the only direct upstream activators of JNK (65).

Animal or cell culture models provided further concrete evidence for a role of JNK2 and JNK3 isoforms, but not JNK1, in regulating the cellular processes involved in Parkinson's pathology (43). Murine knockouts of JNK2 and/or JNK3 underlined the role of these isoforms in the death of dopaminergic substantia nigra neurons (66). Another study by Jing Pan *et al.* (65), demonstrated that specifically JNK3 is activated and translocates from the cytosol to the nucleus following MPTP-induced damage. NAC, an antioxidant agent, which protects neurons from MPTP-induced dopamine death, inhibits JNK3 activation during the early phases of MPTP intoxication, whereas the NMDA receptor antagonist ketamine inhibits JNK3 activation during the late phases of intoxication. This study highlighted the role of oxidative stress in a neurodegenerative disorder such as PD, and supports the hypothesis that targeting the JNK pathway may yield a promising therapeutic approach to combat PD.

Inhibition of JNK with SP-600125, a specific inhibitor of JNK, is effective in MPTP Parkinson's disease model. Adenoviral gene transfer of the JNK-binding domain (JBD) of JIP1 into the striatum inhibits the MPTP-induced JNK activation, the death of dopaminergic neurons in the substantia nigra and has behaviour benefits in an MPTP model of PD (66). On the other hand, clinical studies with an indirect JNK inhibitor CEP-1347, an antagonist of the MAP3K mixed-lineage kinase (MLK) family could not confer neuroprotection in PD patients (67) although it did protect against early events of PD such as neurite degeneration (68). Lee *et al.* (69) suggested that for

complex disorders such as PD, combinational therapies with inhibitors of JNK but also of other major MAPKs involved, such as p38, maybe more efficient in combating PD degeneration.

5.5. Neuroinflammation

Inflammation is becoming an increasingly important aspect of most neurodegenerative disorders (70, 71). Although the inflammatory response may vary to some extent in different diseases still a common spectrum of factors is involved, which includes growth factors, inflammatory cytokines such as interleukin-1 β (IL-1β), tumor necrosis factor (TNF)-a, interleukin-6 (IL-6), chemokines, matrix metalloproteinases (MMPs), lipid mediators and toxic molecules such as nitric oxide.

Accumulating evidence suggest a link between JNKs and inflammation (Figure 1), (for a more detailed review see Kaminska (72). JNKs are expressed in microglia, astrocytes and oligodendrocytes, all cells that dynamically contribute to inflammation (69-72). Initiation of an inflammation response in the brain is marked by microglial activation and an increase of inflammatory cytokines, which on their turn can phosphorylate JNK and subsequently lead to the activation of transcription factors such as NFkB and c-jun (29, 73). At the same time, JNK can regulate the inflammatory response. Microglial cultures stimulated with LPS show rapid and transient (1–3 h) activation of JNK, and a later increase of IL-1h, TNF-alpha, and IL-6 mRNA levels. A determinant role in astrocytic inflammatory response, through regulation of iNOS and TNF, has been assigned to the JNK1 isoform. Similarly, application of both SP600125 and CEP-1347 attenuates the synthesis of proinflammatory cytokines in both human and murine microglia (74). Moreover, CEP-1347 inhibits brain TNF production induced by intracerebroventricular injection of LPS in mice. Importantly, JNKs are also actively involved in the enlargement of activated microglia (74). Such data suggest that JNK inhibitors have anti-inflammatory properties in addition to being potent neuroprotectors.

5.6. Pain

Chronic pain is an important health problem worldwide. In fact, it has been estimated that 20% of the population could be affected by pain in the developed countries. Chronic pain results from neural plasticity manifesting as peripheral and central sensitization and affects various higher brain functions including perception, emotion, cognition, and memory. The mechanisms underlying the induction and maintenance of chronic pain are not completely understood, however, glial activation plays an important role in enhancing and prolonging neural plasticity. Signal transduction pathways regulating pain development and maintenance are beginning to be deciphered. The JNK pathway is activated in primary sensory neurons injury as well as in astrocytes of the spinal cord after nerve injury (Figure 1), (75). At the same time, treatment with D-JNKI-1 prevents mechanical allodynia, produced by spinal nerve ligation, for more than 10 days, while SP600125 can suppress neuropathic pain in diabetic rats (76). Apart from JNKs, other MAPKs such as p38 and ERK contribute to neuropathic pain conditions and play a critical role in microglia signalling (77).

5.7. Brain tumours

Data from Marc A Antonyak *et al.* (78) show that JNKs have a distinct role in the promotion of brain tumorigenesis. JNK, but not ERK, is highly activated in primary human brain tumours (Figure 1). Similarly, EGF, a growth factor that plays an important role in the regulation of cell growth, proliferation and differentiation upregulates JNK activity in brain tumour cell lines but not in normal cells. Inhibition of JNK in those tumour cell lines inhibits EGF mediated anchorage independent growth and resistance to cell death.

6. FUTURE PERSPECTIVES

Treatment of neurodegenerative diseases is a major challenge for neuroscientists since the incidence of these disorders is expected to rise in an ever-increasing aging population.

The past years have established the principal role of JNKs in the pathological processes that characterize neurodegenerative disorders. Concomitantly, several reports have demonstrated that inhibition of JNKs modulates plasticity in the adult CNS. The latter findings render JNK targeting therapies potentially risky since side effects might counterbalance the benefits of a JNK-targeted treatment. Nonetheless the essential role of JNK in neurodegeneration urges the scientific world to overcome the obstacles and unravel the question of how to target the negative "function" of JNKs without affecting the physiological chain. The key to this lock may be on targeting specific JNK-interactions that involve one or more upstream components of the JNK signalling pathway or signalosomes (Figure 2).

Future research should try and elucidate which signalosomes are involved in each pathological situation. Some evidence exists.

For instance, JIP1 and JIP2 only bind to MKK7; these signalosomes are found under basal conditions and increase following ischemia (79) (Figure 2). Interestingly, Centeno *et al.* (80) showed that in cortical neurons, NMDA-induced excitotoxicity involves the activation of MKK7 and not of MKK4 in the JNK signalling pathway. An appealing strategy would be to design a specific inhibitor of MKK7 in order to prevent a single upstream activator of JNK and verify if this will affect just the stress component of JNK signalling pathway, without interfering with the more physiological components of the pathway mediated by MKK4.

On the other hand, JIP3 and JIP4 bind to both MKK7 and MKK4 (81, 82) (Figure 2). Interestingly, JIP3 expression is higher in the brain than in other tissues, binds with high affinity to JNK3 and facilitates phosphorylation of this isoform (81).

Figure 2. JNK's scaffold proteins scheme. Signalling responses are also regulated by scaffold proteins (like JIP1-2-3-4 and β-Arrestin-2) linking JNKs and their upstream activators. In particular, JIP1-2 link only MKK7 and all JNKs, while JIP3-4 bond both MKK7 and MKK4. These JIPs may have different roles in the regulation of JNK signaling response in neurons. JIP3 is strongly expressed in the brain and links predominantly to JNK3, the neuronal JNK isoform. Moreover, another interesting scaffold protein is the *β*-Arrestin-2 that anchors MKK4 and specifically JNK3.

Another interesting signalosome involves the beta-arrestin scaffold protein, which binds to the N-terminus of the JNK3 isoform leading to its specific activation (83), (84) (Figure 2). Beta-arrestin is additionally regulating the subcellular localization of JNK3 thus determining its function (83).

Although further research is required to understand the involvement of the above described signalosomes in neurodegeneration, the emerging role of the JNK3 isoform in a wide range of neurodegenerative disorders, make them interesting targets for the development of drugs that target JNK3 in neurodegenerative disorders.

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