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JNK isoforms control adult mammal hippocampal neurogenesis

Las isoformas JNK controlan la actividad neurogénica hipocampal adulta en mamíferos

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Abstract:

In mammals, the term "Adult Neurogenesis" (AN) defines the process through which, throughout adulthood, new neurons are produced from neural stem cells (NSC). These NSC are located in a specific niche, concretely, in the subventricular zone (SVZ), lining the lateral ventricles, and in the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus. Controversially, new data have questioned the existence of this AN in the human brain seeing how only populations of immature neurons (IN), broadly dispersed within SGZ, have been detected. Either way, neurogenic activity in the hippocampus has been correlated with learning, memory formation and behavioral responses to stress, just like with the pathophysiology of many brain diseases and mood disorders. Various extracellular and intracellular stimuli have been shown to modulate survival, proliferation, and differentiation of adult-bom cells in the hippocampus, especially through conserved stimuli-response mechanisms like the JNKs. In the present review, the JNK pathway and their control of adult hippocampal neurogenesis are described, evidencing the critical role of isoform JNK1.

Keywords:

JNK-pathway, JNK-isoforms, adult-neurogenesis, hippocampus

Resumen:

En mamíferos, el término “Neurogenesis Adulta (NA)”, se define como el proceso a través del cual, en adultos, se producen nuevas neuronas granulares a partir de células madre neurales (CMN). Estas CMN estan ubicadas en microambientes específicos, en concreto en la zona subventicular (ZSV), recubriendo los ventriculos laterales, y en la zona subgranular (ZSG) del giro dentado del hipocampo (GD). Sin embargo, nuevas informaciones han cuestionado la existencia de este proceso de neurogenesis adulta en el cerebro humano, ya que solamente se han detectado poblaciones de neuronas inmaduras (NI) dispersas a lo largo de la ZSG. Independientemente, la existencia de una actividad neurogénica en el hipocampo adulto se ha correlacionado con el aprendizaje, la formación de memoria y en el comportamiento ante situaciones de estrés, así como en la patofisiologia de diferentes patologías del cerebro, incluso en casos de alteraciones del estado de ánimo. Se ha demostrado que diferentes estímulos extracelulares e intracelulares controlan la supervivencia, la proliferación y la diferenciación de las nuevas neuronas del hipocampo, especialmente a través de mecanismos conservados de respuesta a estímulos como las JNKs. En la presente revisión se describe las JNK y su control de la neurogénesis hipocampal adulta, evidenciando el papel crucial de la isoforma JNK1.

Palabras Clave:

JNK-pathway, JNK-isoforms, adult-neurogenesis, hippocampus

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1. GENERAL ASPECTS OF THE JNK PATHWAY.

JNKs are members of a large group of serine/threonine kinases called the mitogen-activated protein kinases (MAPKs). In mammals, three genes, *Jnk1* (MAPK8), *Jnk2* (MAPK9) and *Jnk3* (MAPK10), encode for 10 JNK transcript variants (JNK1α1, JNK1α2, JNK1β1, JNK1β2, JNK2α1, JNK2α2, JNK2β1, JNK2β2, JNK3α1, JNK3α2) which show differential bodily distribution. While JNK1 and JNK2 have ubiquitous tissue distribution, JNK3 is only localized in neurons, heart, and testis.[1-3]

On a functional level, the best-described mechanism linked to the JNKs is their pro-apoptotic action following sustained or intense exposure to cellular stress, such as oxidative, genotoxic and osmotic stress or pro-inflammatory cytokines (TNFα, Tumor necrosis factor; IL-1β, interleukin1β).[4,5] The JNK pathway has a role in many cellular functions linked with human pathologies of varying nature: neurodegenerative and autoimmune diseases, diabetes, cancer, cardiac hypertrophy, and asthma, among others.[5-8] Human genetics studies have evidenced that these kinases are also involved in the pathophysiology of neuropsychiatric disorders.[9-11]

Despite their role in disease development, it has also been described that basal JNK activity may be important in the central nervous system (CNS), both in developmental stages and in adulthood in situations of absence of stress. Specifically, in the mouse brain, JNK activity has been identified to be 17-fold higher compared with peripheral organs.[12] Thus, JNKs are key regulators of brain morphogenesis and developmental death, neuronal migration and pathfinding, axodendritic architecture and synaptic plasticity, with a central role in cognitive function, and protein transport.[13–15]

The JNK pathway is activated following cell exposure to a variety of stress events, such as infection, inflammation, oxidative stress, DNA damage, osmotic stress, or cytoskeletal changes. Different receptors can be activated, including G-protein coupled receptors (GPCRs), Wnt receptors, transforming growth factor-β (TGF-β) receptors, tumor necrosis factor (TNF) receptors, and the Toll receptor complex. Moreover, JNK can be activated in response to endoplasmic reticulum stress (ER stress). It has been suggested that clustering of cytokine receptors could underlie JNK activation in response to UV light or osmotic stress.[16]

The first member of the cascade is the MAPK Kinase Kinase family (MAPKKKs) that phosphorylates and activates members of the MAPK kinase family (MAPKK) which in turn, phosphorylate and activate MAPKs (JNK1/SAPK1, JNK2/SAPK2, and JNK3/SAPK3) (Figure 1). This sequential phosphorylation cascade is facilitated by scaffold JNK-interacting proteins (JIP). Post-translation mechanisms, such as acetylation and ubiquitination of members of the MAPK cascade can also affect MAPK activation, and their inactivation is regulated by MAPK phosphatases (MKPs) within a large group of dual-specificity protein phosphatases (DUSPs) that mediated both positive and negative regulation of the MAPK pathway.[17-20]

1.1. Substrates of the JNKs.

Over 100 proteins are substrates of JNKs can be found all over the cell. Activated molecules may remain in the cytoplasm, nucleus or can be translocated from one compartment to another to exert their function. In the nucleus, the JNKs regulate multiple transcription factors responsible for gene expression. For example, c-Jun, activating transcription factor 2 (ATF2), E26 transformation-specific-like 1 (Elk-1), p53, nuclear factor of activated t-cells 4 (NFAT4) and other chromatin modifiers.[17,21,22] In the cytoplasm, they control microtubule-associated proteins such as MAP1B, MAP2, Doublecortin (DCX) and superior cervical ganglion 10 protein (SCG10; also known as STMN2), phosphatases, cytoskeletal associated protein receptors, apoptosis-related proteins, among others (Figure 1).[3,17] In neurons, specific substrates can be found in dendrites, axons, and presynaptic endings.[17,22] The existence of all these substrates explains the wide range of JNK-controlled biological functions.

1.2. Distribution of the JNKs in the brain.

The JNK isoforms show divergent distribution patterns in the central nervous system (CNS) of mammals. Initial descriptions of their localization stated that the *Jnk3/SAPKβ* mRNA transcripts were the most highly expressed in the rat adult brain, followed by *Jnk2/SAPKα*, mainly located in the neocortex, hippocampus, thalamus, and midbrain and finally by *Jnk1/SAPKγ*. It was determined that JNK1 mRNA expression decreased as development proceeded, is mainly localized in the endopiriform nucleus, medial habenula, and hippocampus. Interestingly, *Jnk1/SAPKγ* mRNA levels remained high in the plastic olfactory area throughout adulthood.[23] Controversially, this distribution for the *Jnk1/SAPKγ* transcripts did not correlate with the results obtained in the adult mouse brain by Lee et al., who described high immunoreactivity for JNK1/SAPKγ and JNK3/SAPKβ in most cerebral cortical regions. The authors identified JNK3/SAPKβ isoform in 30% of cortical neurons and 90% of hippocampal neurons while JNK1/SAPKγ isoform was detected mainly in CA3 and CA4 hippocampal areas. In the cerebellum, they determined high JNK3/SAPKβ immunoreactivity in the cell body of Purkinje cells and granular neurons, while JNK1/SAPKγ was localized in the molecular layer of the cerebellum. Regarding JNK2/SAPKα, moderate levels were identified in trigeminal, vestibular and facial nuclei of the brain stem and in the deep nuclei of the cerebellum.[24]

The different distribution of the JNK isoforms, together with their distinct subcellular localization and the variety of cytosolic and nuclear substrates suggest that they may have specific and highly varied functions. The use of knockout models has allowed for important discoveries, both in understanding better brain development[25-28], pathologies[3,29–32] and the role of the JNKs in them.

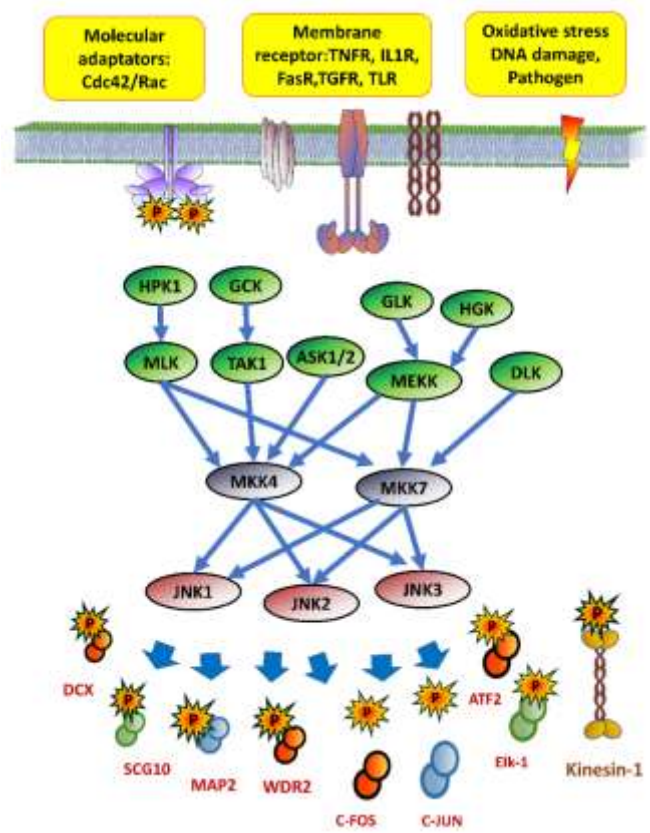

Figure 1. Representative model of the JNK cascade signaling. MAPK signaling is represented as a bow-tie of three different tiers or modules in the core of the cascade. These modules represent MAP3K, MAP2K and MAPK families. A repertoire of sensory proteins (membrane receptors and molecular adapters) receives a variety of stimuli, commonly from an extracellular signal in the proximity of the cellular membrane activating the MAP3K family. MAP4K is an extra module upstream to MAP3K that can be activated by membrane receptors. MAP4K is represented by HPK (hematopoietic progenitor kinase); GCK (Germinal Center Kinase), GLK (Germinal Center Kinase-Like Kinase), HGK (hepatocyte progenitor kinase-like / germinal center kinase-like kinase). MAP3Ks are represented by the MLK (the mixed-lineage kinase), TAK (transforming growth factor β-activated kinase), ASK (apoptosis signal-regulating kinase), MEKKs (MAPK / ERK Kinase Kinase) and DLK (Dual Leucine Zipper Kinase) and their different isoforms. MAP2K is represented by two members, MKK4 and MKK7. MAPK contains only one member and has three different isoforms (JNK1, JNK2, and JNK3). JNK phosphorylates microtubule and actin-associated proteins that regulate migration and the axodendritic process.

2. JNKS AND ADULT HIPPOCAMPAL NEUROGENESIS.

Newborn neurons in the adult hippocampus are necessary to maintain normal cognitive functions like learning, memory, and adaptation to changing environments. Moreover, several brain diseases, such as neurological diseases and mood disorders have impaired hippocampal neurogenesis.[32,33] Thus, there has been continuous effort to study any mechanisms linked to these responses, so that new therapeutic strategies that employ hippocampal neural stem cells (NSCs) may be developed. Over the years, different reports have supported that JNKs have a role in the control of adult hippocampal neurogenesis.[11,13,34] In the present review, it is emphasized the role of JNKs into the control of neurogenesis in the hippocampus, with a special focus on isoform JNK1.

2.1. Adult neurogenesis in the hippocampus of mammals

The generation of new neurons from stem and precursor cells in the central nervous system (CNS) was believed to occur only during embryonic and early postnatal development stages in mammals. However, at the beginning of the 20th century, mitotic activity in the walls of the lateral ventricle of the adult brain was discovered.[35] Subsequent studies in young rats demonstrated the existence of mitotic cells in the ependymal and subependymal layers of the third and lateral ventricles, just like the presence of a group of undifferentiated cells near the granular layer (GL) of the dentate gyrus (DG) (Figure 2). It was postulated that these undifferentiated cells migrate postnatally from the forebrain ventricles to the hippocampus where they differentiate.[36] Although the existence of adult hippocampal neurogenesis was discovered in 1975 by Joseph Altman, the concept of functional hippocampal neurogenesis began to emerge around 1990.[37–39] The adult neurogenesis process (AN) implies the existence of the active stem cells located in specific niches that produce new neurons that are subsequently integrated into old circuits through life. In mammals, this process is restricted to regions of the paleocortex (olfactory bulb, OB), archicortex (hippocampus) and the periventricular germinal layer in the hypothalamus.[40]

Briefly, new neurons are originated from neural stem cells (NSC) that extent radial processes and express biomarkers typical of their neuroepithelial origin, like the glial fibrillar acidic protein (GFAP). Due to these features, NSCs are called radial glia like-cells (Figure 3A). NSCs proliferate and generate other differentiated progenitors with high proliferative capacity (Figure 3B).[41–45] Appropriate stimuli from the environment or internal cues stimulate the progress of neuronal NSC determination, characterized by the loss of glial-radial projections and the expression of DCX, a microtubule-associated protein (Figure 3B, C, and D). The second phase is characterized by morphological differentiation such as dendritic and axonal extension, spine maturation, cessation of mitotic division and migration to the granular cell layer and the hilus (Figures 2 and 3).[40]

Granule cells are the main excitatory neurons of the DG. They receive input from the entorhinal cortex and send their axonal projection along the mossy fiber tract to pyramidal cells of the *cornu ammonis 3* (CA3) area. They fire very sparsely and their activity is modulated by a large number of interneurons in the DG and hilus area.[46]

It is important to mention that newly-produced cells are not destined to fully and continuously replace old granular cells, but rather to provide new elements to complete the functional role of DG, as it occurs in other tissues (epidermis or bone marrow for example). A reduction in the rate of neurogenesis with age is correlated with cognitive decline.[47]

In humans, AN has only been described a few times in the SGZ of DG of the hippocampus. One of them was done by Moreno-Jimenez et al. who evidenced the presence of immature neurons (DCX^+) in the DG of humans aged up to 90 years under controlled conditions of postmortem tissue fixation.[48] Not many studies have been able to identify substantial rates of cell proliferation or a recognizable niche-like histological structure.[49,50] This situation has lead to the idea that its existence is dubious and debatable even though it is known that this process has a prominent role in the maintenance of cognitive function. The treatment of postmortem tissue might be masking their discovery.[33,50,51]

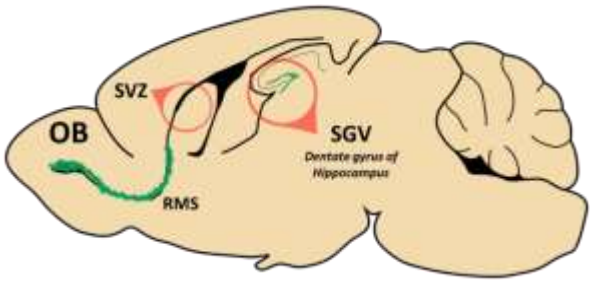

Figure 2. There are two places where the adult neurogenesis occurs in rodents, subventricular zone (SVZ) of the lateral ventricles and subgranular zone (SGZ) of the granule cell layer of the DG of the hippocampus. Progenitors migrate from SVZ to the olfactory bulb (OB) forming the rostral migratory stream (RMS). Meanwhile, progenitors migrate locally into SGZ through GCL. Sagittal section of a mouse brain made by Jonas Töle under license Creative Commons CC0 1.0.

Ultimately, the difficulty to identify the AN process in hippocampal humans leads to the appearance of different interpretations of the nature and function of these undifferentiated cells defined as "immature neurons" (IN). For now, it seems that they are broadly distributed in the putative *SGZ* (*human subgranular area*) and hilus, and have a slow rate of neuronal maturation, explaining the few proliferative events detected in the human hippocampus.[40] This theory would imply that IN are not newly generated, but rather are static there and may replace the adult neurogenic process that occurs in rodents and other vertebrates, representing an evolutionary choice in large-brained mammals as an alternative form of plasticity.[40] These IN, in addition to being found in the hippocampus, have been located in other brain areas like the neocortex and several subcortical regions in large-brains.[52]

Despite these controversies in the existence of clear AN in the human hippocampus, a decrease in neurogenesis rate has been detected in several pathologies like depression or Alzheimer's disease.[53] Antidepressant therapy or exercise has been described to have a positive effect to ameliorate behavioral phenotypes by promoting neurogenic activity.[54-56] Specifically, Chohan et al. discovered that the peripheral administration in normal adult mice of an *11-mer peptide (Peptide 6)* designed from an active region of the human ciliary neurotrophic factor (CNTF), induced an increase of proliferation of neural progenitor cells and their differentiation into neurons. These changes were correlated with memory affectations.[57] Thus, further research must be done to determine the presence and roles of hippocampal neurogenesis in psychiatric diseases and neurodegenerative disorders.

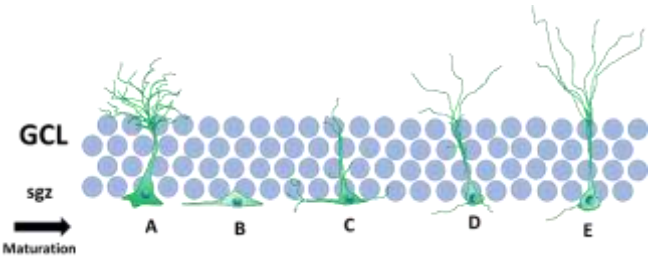

Figure 3. Progenitors from GCL are committed to becoming mature granule neurons after experiencing changes in their morphology. First, glial radial like-cells (a) progress to immature neurons (b, c, d). immature neurons migrate through GCL expressing cellular markers as DCX and PSA-NCAM. In the last stages of maturation, immature neurons (d) define their axon and dendritic trajectories into the hippocampal circuit and gradually lose the expression of immature neuron markers and acquire a neuronal phenotype (E).

2.2. JNK pathway has a role in the control of adult hippocampal neurogenesis.

Recently, anomalies on the activity of the JNK pathway have been associated with alterations in adult hippocampal neurogenesis. Sun et al. evidenced that high levels of JNK and p38 phosphorylation are correlated with a decrease in adult hippocampal neurogenesis.[56] It was also demonstrated that the intrastriatal administration of FAK14, an inhibitor of focal adhesion kinase, induced a reduction of phosphorylated JNK together with an increase in the neurogenesis in the SVZ. This increase was associated with the activation of astrocyte-derived ciliary neurotrophic factor (CNTF). Thus, the FAK–JNK–CNTF pathway could be a specific target to promote neurogenesis.[58]

In this manner, results obtained in our group support the role of JNK in the control of neurogenesis in adult mice. Specifically, in *Jnk1*$^{-/-}$ mice the number of proliferative immature neurons, DCX^+ cells (Doublecortin) and PSA-$NCAM^+$ cells (Polysialylated neuronal cell adhesion molecule) were higher than in WT.[34] Contrarily, the lack of JNK1 induced a decrease in the number of early precursor cells[34] (glial fibrillary acidic protein, $GFAP^+$, and transcription factor $Sox2^+$) as it occurs with the absence of JNK3. Altogether, this data supported the idea that these enzymes have a role in the adult hippocampal neurogenic activity with a clear effect of JNK1 in enhancing the rate of proliferation without proper self-renewal, which may promote the extinction of the pool of neuronal precursors. Mohamed et al. also observed an increase in hippocampal neurogenesis in mice lacking *Jnk1*. This enhancement was characterized by a higher rate in cell

proliferation, evaluated with 5-Bromo-2'-deoxyuridine, BrdU (an analog of thymidine) cell number and Ki67 positive cell, as indicators of cell division; cell survival, analyzing the cell death (positive for cleaved caspase-3; cysteine-aspartic acid protease) and the increase of immature neurons: DCX^+ cells and $BrdU^+/NeuN^+$ (nuclear antigen used as biomarkers of neurons) cells. The same behavioral phenotype that was detected in mice lacking JNK1 was observed in mice treated with intracerebroventricular infusion of a peptide inhibitor of JNK (DJNK1-1, chemically identical to XG-102) that was delivered only in immature granule cells, however in this case without an increase of hippocampal neurogenesis.[11]

All these findings support the idea that JNKs have a role in the control of the hippocampal neurogenic niche, specially JNK1 that has control in the rate of immature neurons proliferation. This effect was supported by the rapid proliferation rate observed in embryonic stem cells (ESC) from *Jnk1*$^{-/-}$ *Jnk2*$^{-/-}$ mice compared to wild type embryonic stem cells. Beside, ESC from Knockout mice exhibited alterations in lineage-specific differentiation.[59]

Controversially, the opposite effect of JNK1 was observed in carcinogenesis. For example, silencing JNK1 by siRNA represses the growth of childhood sarcoma, thus indicating that this isoform also has a pro-proliferative role; its ablation has also been associated with the reduction of lung tumors.[60] In this line, mice lacking JNK1 exhibited a marked decrease in gastric carcinogenesis induced by N-methyl-N-nitrosourea, compared to their wild-type counterparts.[61] The same occurs with the lack of *Jnk1* in a mouse hepatocellular carcinoma induced by diethylnitrosamine.[62] These controversial effects of JNK1 in adult hippocampal neurogenic niches and tumor cells may respond to the existence of different signal interactions in each environmental condition or cell origin. Additionally, the dendritic field size of immature granule neurons increased in *Jnk1*$^{-/-}$ mice, coupled with an enhancement in the levels of NR2B, a subunit of the NMDA receptors, facilitating synaptic plasticity of newborn neurons.[11,63] Probably these changes can explain the low anxiety phenotype observed in *Jnk1*$^{-/-}$ mice and highlight that the modulation of JNK1 activity could be a good strategy for the treatment of pathologies like depression or anxiety, just like neurodegenerative diseases, stroke, cancer and inflammatory diseases.[6,8,64,65]

2.3. Regulatory role of JNK signaling in neuronal survival and differentiation.

JNKs besides regulating physiological and pathological processes in the central and peripheral nervous system have a critical role in the control of neural proliferation, differentiation, viability, and structural integrity. All these processes are essential for maintaining synaptic connections and neural plasticity. Despite having different studies with *in vitro* models, the role of the JNK pathway in these biological processes is still unknown. Here, we current knowledge on different substrates of JNKs that may control these processes is summarized, just like those additional factors that control JNK activity when trying to promote neuronal survival and differentiation.[65-75]

Mouse embryonic neural stem cells (NSC) were treated with an anticonvulsant drug, valproic acid, who induced c-Jun phosphorylation by JNK, promoting neuronal differentiation of mouse embryonic NSCs and neurite outgrowth of NSC-derived neurons. Additionally, the use of a specific JNK inhibitor (SP600125), substantially decreased neurite outgrowth of NSC-derived neurons.[66] The treatment with retinoic acid of mouse embryonic stem (ES) cells, also supported the role of JNK activation in neuronal differentiation. Concretely, through the activation of STAT1/3 transcription factors. This JNK effect was reinforced with the SP600125 treatment on NSC because the neurite outgrowth, during the differentiation and maturation stages, was inhibited. Also, this study highlighted the role of JNK3 during ESC neuronal commitment and in early neural development.[67] In another work, with cultures of adult mouse dorsal root ganglion (DRG) neurons, it was evidenced that JNK1 and JNK2 were needed for axonal elongation by regulating the phosphorylation state of MAP1B, a cytoskeletal kinase needed for sprouting or regenerating axons.[68] In the same line, Atkinson et al. treated spiral ganglion neurons cultures with neurotrophic factors that activated JNK; activation, locally in the growth cones, induced neurite outgrowth through the phosphorylation of MAP1B and MAP2.[69] Using PC12 in vitro neuronal model, Vicki et al. reported the role of JNK to promote neuron survival and neurite stability through the activation of the transcription factor 3 (ATF3).[70] Treatment of these cells with neurotrophic factors revealed that JNK-interacting protein 3 (JIP3) may be involved in the transport of vesicular cargo to the growth cones, possible targeting JNK to paxillin substrate facilitating neurite outgrowth.[71]

Adding neurotrophic factor in embryonic sympathetic neurons and PC12 cells allowed the identification of Dual-specificity protein phosphatases (DUSPs), that selectively dephosphorylates JNK, as a key regulator to maintain neuronal survival differentiation and synaptic plasticity.[72]

Moreover, it has been reported that pro-inflammatory cytokines who are expressed in diverse neurodegenerative and neuroinflammatory conditions have a role in promoting neuronal plasticity and cell survival. In this line, the action of the interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNFα) in enhancing neurite outgrowth of PC12 cells has been evidenced after nerve growth factor (NGF) stimuli.[73] Concretely, in C17.2 neural progenitor cells (isolated from the neonatal mouse cerebellum), it was elucidated that JNK signaling participates in neuronal differentiation in response to IFN-γ.[73] Moreover *in vivo* studies with transgenic mice expressing limited amounts of IFN-γ on the adult brain (levels that not cause gliosis or tissue abnormalities) revealed an increase in proliferation and differentiation in the dentate gyrus of the hippocampus, associated with neuroprotection and improved spatial cognitive

performance.[74] Despite this effect of IFN-γ in neurogenesis, it must be mentioned that its therapeutic benefits would be a consequence of the activity of other accompanying cytokines and chemokines, both in physiological conditions and in an inflammatory response.[75]

In conclusion, in the present review, it has been evidenced the role of the JNK pathway in the control of neuronal proliferation, differentiation, and survival, with a special focus on JNK1 in the regulation of adult hippocampal neurogenesis in rodents. Moreover, the review questions the existence of the adult neurogenic process in humans, assuming that in large brains there is another form of brain plasticity associated with the presence of immature neurons in the hippocampus and also in other brain areas. It has also been introduced that adult neurogenesis is altered in different diseases. Altogether, the fact that JNKs have a wide arrange of possible actions that may vary due to multiple factors, makes it essential to continue researching the individual JNKs activity so that they can be used as effective therapeutic approaches.

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